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INTERMEDIATE ACTION OF MIXTURES OF SOLUBLE INSULIN AND PROTAMINE ZINC INSULIN

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From the standpoint of clinical usefulness in cases of severe diabetes neither of the two standard insulins, soluble insulin and protamine zinc insulin, is ideal for routine day by day use. Because it is in solution, ordinary insulin is absorbed rapidly and within a short time exerts a strong effect which fades quickly. Hence it must be given frequently, and in excess it tends to cause violent hypoglycemic symptoms. With soluble insulin alone it is impossible to control severe diabetes in many cases unless multiple daily injections are given, including one during the normal sleeping hours. The same is true of solution of zinc insulin crystals, or crystalline insulin, the action of which is practically identical with that of ordinary insulin.[1]

Protamine zinc insulin eliminates some of these disadvantages because it releases insulin slowly. Its effects are slow in onset, weak until reenforced by repeated overlapping doses but slow to disappear.[2] Hence, even severe diabetes can be better controlled by injections given

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1. Jackson, R. L., and Boyd, J. D.: Relative Efficiency of Commercial Forms of Insulin, Proc. Soc. Exper. Biol. & Med. **41**:15-16 (May) 1939. Marble, A., and Vartiainen, I.: Crystalline Insulin, J. A. M. A. **113**:1303-1309 (Sept. 30) 1939. Ricketts, H. T., and Wilder, R. M.: Solutions of Amorphous Insulin and Solutions of Zinc Insulin Crystals: Clinical Studies of Comparative Speed and Duration of Action, ibid. **113**:1310-1312 (Sept. 30) 1939. Duncan, G. G.; Cuttle, T. D., and Jewesbury, E. C. O.: Observations on Comparative Clinical Values of Zinc Insulin Crystals in Solution and Unmodified Insulin, Bull. Ayer Clin. Lab Pennsylvania Hosp. **3**:293-306 (Dec.) 1939.

2. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **59**:329-337 (Feb.) 1937.

once daily; hypoglycemia is not so violent or frequent; glycosuria during overnight fasting is modified; sudden acidosis is less likely to occur with delays in its administration, and general health and nutrition are better because of its more sustained action.[3] Yet it possesses two major disadvantages, both due to slow or uncertain absorption. First, there are inconsistencies in the responses to repeated daily doses of the same size, probably due to variations in the rates of solution and absorption of insulin from different depots. This produces an undulating form of control, with unpredictable waves of glycosuria and of hypoglycemia.[4] Second, in cases of severe diabetes doses of protamine insulin sufficiently large to control the glycosuria following generous carbohydrate meals are likely to cause hypoglycemic shock during the night period of fasting. Doses small enough to avoid nocturnal hypoglycemia tend to permit heavy glycosuria after meals.[5]

The combined use of both standard insulins stands out as the method of therapy which most uniformly avoids the problems inherent in treatment with either type of insulin alone. Most often this is accomplished by injection of one large dose of protamine zinc insulin daily and one or two supplementary smaller doses of soluble insulin.[6] Thus, the prolonged, fairly uniform action of protamine zinc insulin in an amount sufficient to control nocturnal glycosuria is supplemented by small doses of soluble insulin which modify the heavier glycosuria following meals and fade out during the night when not needed. Probably combined treatment with both types of insulin injected separately is the most common in use today by patients with severe diabetes. Its rationale has recently been considered in illuminating detail by Peck.[7]

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3. Joslin, E. P.: Protamine Insulin and Its Advantages, New England J. Med. **215**:1166-1168 (Dec. 17) 1936.

4. Joslin, E. P.: Difficulties in the Use of Protamine Zinc Insulin, J. A. M. A. **110**:90-91 (Jan. 8) 1938. Kepler, E. J.: Clinical Experience with Protamine Zinc Insulin, ibid. **110**:92-96 (Jan. 8) 1938. Mark, M. F.: Optimum Time for Administration of Protamine Zinc Insulin, Arch. Int. Med. **64**:897-906 (Nov.) 1939.

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6. (*a*) Campbell, W. R.; Fletcher, A. A., and Kerr, R. B.: Protamine Insulin in the Treatment of Diabetes Mellitus, Am. J. M. Sc. **192**:589-600 (Nov.) 1936. (*b*) Joslin, E. P.; Root, H. F.; Marble, A.; White, P.; Joslin, A. P., and Lynch, G. W.: Protamine Insulin, New England J. Med. **214**:1079-1085 (May 28) 1936. (*c*) Joslin, E. P.: Protamine Insulin, J. A. M. A. **109**:497-503 (Aug. 14) 1937. (*d*) Warvel, J. H., and Shafer, M. R.: Protamine Insulin in the Treatment of Diabetes Mellitus, J. Indiana M. A. **30**:325-332 (July) 1937. (*e*) Mosenthal, H. O.: Protamine Zinc Insulin: Clinical Application, J. A. M. A. **110**:87-90 (Jan. 8) 1938.

7. Peck, F. B.: Therapeutic Application of the Various Insulins, South. Med. & Surg. **103**:539-545 (Oct.) 1941.

Although that method provides better control than the use of either insulin alone, multiple injections still are required. Many patients with more severe forms of diabetes still find it difficult to avoid intermittent hypoglycemia and glycosuria. Confusion is created by the use of two preparations with different properties. Most efforts to mix them have failed in their purpose, because a small proportion of soluble insulin is precipitated by the excess free protamine in protamine zinc insulin and its prompt effect is lost.[8]

MIXTURES OF SOLUBLE INSULIN AND PROTAMINE ZINC INSULIN

With few exceptions previous work with mixtures of the two standard insulins has been confined to uncritical use of them mixed in the proportions commonly employed in practice, i. e., large doses of protamine zinc insulin combined with smaller doses of insulin in the same ampule or syringe. Lawrence expressed the belief that mixtures containing as little as 12 units of soluble insulin in 40 units of protamine zinc insulin might lose some of the soluble insulin by precipitation [9] but retained the individual actions of both types of insulin.[10] Graham [11] used larger fractions of soluble insulin, but protamine zinc insulin was still in excess. Wilder and his associates advised against the use of such mixtures [8] but later "adopted this technic with results that are very satisfactory." [12]

A few investigators have attempted to avoid loss of soluble insulin on mixing by using a narrow bore [6a] or double-barrelled [13] syringe or by employing separate syringes attached successively to the same needle *in situ*.[14] These methods obviously do not avoid contact before or after injection and hence permit mixing in variable degrees.

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8. Sprague, R. G.; Blum, B. B.; Osterberg, A. E.; Kepler, E. J., and Wilder, R. M.: Clinical Observations with Insulin Protamine Compound, J. A. M. A. **106**: 1701-1705 (May 16) 1936.

9. Lawrence, R. D.: The Treatment of Insulin Cases by One Daily Injection, Acta med. Scandinav., 1938, supp. 90, pp. 32-53.

10. Lawrence, R. D.: Zinc-Protamine-Insulin in Diabetes: Treatment by One Daily Injection, Brit. M. J. **1**:1077-1080 (May 27) 1939.

11. Graham, G.: The Use of a Mixture of Ordinary and Protamine Insulin, Acta med. Scandinav., 1938, supp. 90, pp. 54-63.

12. Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1940, p. 92.

13. Watson, E. M.: A Double Syringe for the Administration of Protamine Zinc and Unmodified Insulin, Canad. M. A. J. **40**:72-73 (Jan.) 1939.

14. Campbell, W. R.: Some Difficulties in the Use of the Insulins in Diabetic Practice, Bull. New York Acad. Med. **15**:579-596 (Sept.) 1939. Starch in Gluten Bread-Mixtures of Different Types of Insulin, Queries and Minor Notes, J. A. M. A. **112**:871 (March 4) 1939.

More critical studies have shown that mixtures containing small amounts of soluble insulin act in a manner indistinguishable from that of protamine zinc insulin. Bjuggren [15] reported that the action of morning doses of ordinary mixtures was weaker during the day but stronger at night than that of separate doses of the same quantities, probably because part of the regular insulin was converted into protamine zinc insulin on mixing. A well controlled comparison by Masters [16] showed that such mixtures act like protamine zinc insulin. Hence, most authorities now are reluctant to use such mixtures and advise separate injections when both insulins are required in cases of severe diabetes.[17]

Some observers [18] obtained more consistent and encouraging results by increasing the proportions of soluble insulin in the mixtures. Ulrich [19] recognized the difficulties inherent in mixing the two standard types of insulin. The excess of free protamine in commercial protamine zinc insulin readily combines with soluble insulin added to it. Thus, the net result, up to a certain limit of added insulin, is conversion into protamine insulin, with action identical with the action of that substance. Ulrich secured some modification of effect by mixing the two types in equal proportions. When more than an equal amount of soluble insulin was added, unmistakable increases in prompt action were obtained, comparable to those resulting from large doses of protamine zinc insulin and smaller doses of soluble insulin injected separately. Mixtures containing three parts soluble insulin and two parts protamine zinc insulin seemed most promising for clinical use in suitable patients. The action of repeated doses was fairly consistent and predictable—in fact, more so than that of separate injection of the two components simultaneously.

OTHER INSULIN COMBINATIONS WITH SUSTAINED EFFECTS

Literally dozens of other insulin combinations with prolonged action have been described in the literature—most of them within the past six years. To undertake a critical appraisal of their merits would be impossible for lack of comparative data. Few have been compared with

15. Bjuggren, S.: Question of Mixing Common Insulin with Protamine Zinc Insulin Before Injection, Nord. med. (Hygiea) **4**:3099-3101 (Oct. 14) 1939.

16. Masters, T. D.: The Use of the Newer Insulins, Illinois M. J. **78**:319-323 (Oct.) 1940.

17. Morris, N.: The Newer Insulins, Glasgow M. J. **133**:1-19 (Jan.) 1940. Watson, E. M.: Comparative Efficiency of Various Methods for Administering Insulin, Canad. M. A. J. **43**:444-447 (Nov.) 1940. Marble, A.: The Treatment of Diabetes with Diet and Insulin, New England J. Med. **224**:583-586 (April 3) 1941.

18. Wauchope, G. M.: Zinc Protamine Insulin and Soluble Insulin Interaction in Combined Doses, Lancet **1**:962-966 (May 25) 1940. Graham.[11]

19. Ulrich, H.: Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulins, Ann. Int. Med. **14**:1166-1179 (Jan.) 1941.

each other, although many were compared with insulin or with protamine zinc insulin by a variety of methods. An excellent review of those studied before 1938 is contained in Jensen's monograph on insulin.[20] A summary of the types of combinations, their names, the dates of report, the investigators and the distinguishing characteristics is contained in table 1.

Originally, it was hoped that the addition of zinc would give a desirable intermediate action to soluble insulin. The introduction of solution of zinc insulin crystals was accompanied by claims of prolonged effect.[22] Undoubtedly, zinc lengthens slightly the duration of action both of soluble and of protamine insulin,[23] but the difference is not of practical importance. There is still a wide spread between the intensity and the duration of the action of the two standard types of insulin in spite of the addition of zinc. The chief value of solution of zinc insulin crystals lies in its freedom from foreign protein.

Histone insulin,[24] globin insulin[25] and acid, or clear, protamine insulin[26] are the modifications which appear most promising. A

20. Jensen, H. F.: Insulin: Its Chemistry and Physiology, New York, Oxford University Press, 1938, pp. 97-103.

21. Footnote deleted by author.

22. Freund, H. A., and Adler, S.: Effects of Standard, Protamine and Crystalline Insulin on Blood Sugar Levels, J. A. M. A. **107**:573-577 (Aug. 22) 1936. Mains, M. P., and McMullen, C. J.: The Clinical Investigation of an Improved Crystalline Insulin: Preliminary Report, ibid. **107**:959-962 (Sept. 19) 1936.

23. (*a*) Scott, D. A., and Fisher, A. M.: Studies on Insulin with Protamine, J. Pharmacol. & Exper. Therap. **58**:78-92 (Sept.) 1936. (*b*) Kerr, R. B.; Best, C. H.; Campbell, W. R., and Fletcher, A. A.: Protamine Insulin, Canad. M. A. J. **34**:400-401 (April) 1936. (*c*) Rabinowitch, I. M.; Foster, J. S.; Fowler, A. F., and Corcoran, A. C.: Clinical Experiences with Protamine-Zinc-Insulin and Other Mixtures of Zinc and Insulin in Diabetes Mellitus, ibid. **35**:239-252 (Sept.) 1936. (*d*) Drysdale, H. R.: Protamine Insulin in Juvenile Diabetes: Clinical Observations, J. A. M. A. **108**:1250-1257 (April 10) 1937. (*e*) Smith, B., and Grishaw, W. H.: Survey of Diabetes: Statistical Data and Control Comparisons with Various Insulins, Arch. Int. Med. **66**:465-477 (Aug.) 1940.

24. (*a*) Bischoff, F.: Histone Combinations of the Protein Hormones, Am. J. Physiol. **117**:182-187 (Sept.) 1936. (*b*) Gray, P. A.; Bischoff, F., and Sansum, W. D.: Treatment of Diabetes Mellitus with Insoluble Insulin Compounds: Histone-Insulin, Ann. Int. Med. **11**:274-284 (Aug.) 1937.

25. (*a*) Reiner, L.; Searle, D. S., and Lang, E. H.: Insulin Preparations with Prolonged Activity: Globin Insulin, Proc. Soc. Exper. Biol. & Med. **40**:171 (Feb.) 1939. (*b*) Bauman, L.: Clinical Experience with Globin Insulin, Am. J. M. Sc. **198**:475-481 (Oct.) 1939. (*c*) Marks, H. E.: A New Globin Insulin, M. Clin. North America **24**:649-670 (May) 1940. (*d*) Duncan, G. G., and Barnes, C. E.: The Action of Globin Insulin Compared with That of Crystalline, Unmodified and Protamine Zinc Insulin, Am. J. M. Sc. **202**:553-563 (Oct.) 1941.

26. Warvel, J. H.: Protamine and Other Slow Acting Insulins and Their Clinical Application: Review of Medical Progress, Ohio State University College of Medicine, 1940, p. 140.

TABLE 1.—*Insulin Combinations with Sustained Effects*

Compound	Comment	Author
	Lipoid Suspensions and Emulsions	
Metacholesterin, "oil," liquid petrolatum or hydrous wool fat and insulin	Viscous mixtures; uncertain absorption	Bernhardt and Strauch: Ztschr. f. klin. Med. **104**: 744, 1926
Arachis oil or castor oil and insulin	Viscous mixtures; uncertain absorption	Leyton: Lancet **1**: 756, 1929
Cholesterol and insulin	Uncertain action	Lange and Schoen: Arch. f. exper. Path. u. Pharmakol. **113**: 92, 1926 Surányi and Szalai: Klin. Wchnschr. **9**: 2159, 1930
Lecithin and insulin	Uncertain action	Surányi and Szalai: Klin. Wchnschr. **9**: 2159, 1930 Skouge: Acta med. Scandinav. (supp.) **50**: 232, 1932
Colloid system containing insulin (insulin-durant)	Two or three day hypoglycemic effects	Katsch, Scholderer and Klatt: Ztschr. f. klin. Med. **129**: 608, 1936 Klein and Grosse: Ztschr. f. d. ges. exper. Med. **98**: 623, 1936 Störring: Med. Klin. **1**: 369, 1937
	Colloid Combinations	
Acacia and insulin	Some prolongation of effect	Burgess, Campbell, Osman, Payne and Poulton: Lancet **2**: 777, 1923 Redisch and Block: Endokrinologie **1**: 241, 1928
Gelatin and insulin	Uncertain action	Lange and Schoen: Arch. f. exper. Path. u. Pharmakol. **113**: 92, 1926 Thiel, Ruhnau and Unger: Deutsche med. Wchnschr. **60**: 975, 1934
Surfen insulin	Comparable in action to protamine zinc insulin	Umber, Störring and Föllmer: Klin. Wchnschr. **17**: 443, 1938 Umber, Störring and Giet: Klin. Wchnschr. **17**: 190, 1938 Martin: Ztschr. f. d. ges. exper. Med. **105**: 599, 1939 Holland and Weyer: Zentralbl. f. inn. Med. **61**: 72, 1940 Schramm: Klin. Wchnschr. **19**: 470, 1940
Heavy metals, basic compounds and insulin	Retarded action	Jensen: Insulin: Its Chemistry and Physiology, New York, Oxford University Press, 1938, p. 101
Pectin and insulin	Uncertain action	Wuhrmann: Schweiz. med. Wchnschr. **69**: 1275, 1939
	Protein Combinations	
Protamine insulin	Standard in clinical practice	Hagedorn, Jensen, Krarup and Wodstrup: J. A. M. A. **106**: 177 (Jan. 18) 1936
Acid protamine insulin	Maximum effect in 8 to 10 hours but inconsistent response	Warvel [26] Bailey and Marble [27]
Protamine insulin pellets	Duration of effect 44 to 100 hours	Mark and Biskind: Endocrinology **26**: 444, 1940
Histone insulin	Action comparable with that of protamine insulin	Bischoff [24a] Gray, Bischoff and Sansum [24b] Bailey and Marble [27] Barnes, Cuttle and Duncan: J. Pharmacol. & Exper. Therap. **72**: 331, 1941
Globin insulin	Action intermediate between that of soluble and of protamine insulin	Reiner, Searle and Lang [25a] Bauman [25b] Marks [25c] Andrews and Groat: New York State J. Med. **40**: 913, 1940 Duncan and Barnes [25d] Bailey and Marble [27]
Arginine insulin	Similar in action to protamine insulin	Vartiainen and Bastman: Acta med. Scandinav. **98**: 318, 1939

TABLE 1.—*Insulin Combinations with Sustained Effects—Continued*

Compound	Comment	Author
	Mixtures with Vasoconstrictors	
Extract of posterior pituitary and insulin (deposulin)	Delayed but inconsistent effect	Zirwer: Klin. Wchnschr. **16**: 1121, 1937 Martin: Ztschr. f. d. ges. exper. Med. **105**: 599, 1939 Holland and Weyer: Zentralbl. f. inn. Med. **61**: 72, 1940 Schweers: Klin. Wchnschr. **16**: 392, 1937 Taeger and Danish: Klin. Wchnschr. **16**: 1639, 1937 Beckmann and Weitzsäcker: Klin. Wchnschr. **17**: 1321, 1938
Epinephrine and insulin	.....	Beckmann and Weitzsäcker: Klin. Wchnschr. **17**: 1321, 1938
	Inorganic Modifications	
Ferric chloride and insulin	Augmentation of response	Maxwell and Bischoff: Am. J. Physiol. **112**: 172, 1935
Zinc and regular insulin or protamine insulin	Prolongation of action of insulin and of protamine insulin	Scott and Fisher [22a] Kerr, Best, Campbell and Fletcher [22b] Rabinowitch, Foster, Fowler and Corcoran [22c]
Tannic acid and insulin	Local reactions	Gray: Endocrinology **20**: 461, 1936
New fraction of pancreas extract with added magnesium chloride (nativ-insulin-depot)	.....	Umber, Störring and Engelmann: Klin. Wchnschr. **18**: 837, 1939 Beckmann and Weitzsäcker: Med. Klin. **36**: 376, 1940
Alum-precipitated insulin	Peak effect in 8 to 12 hours	Rosenthal, Fialka and Kamlet: Am. J. M. Sc. **198**: 98, 1939
	Miscellaneous Combinations	
Safranin and insulin	Prolonged action	Jacobs and Ricketts: Proc. Soc. Exper. Biol. & Med. **35**: 473, 1936
Methenamine and insulin	Clear mixture which precipitates on injection; intermediate effect	Feinblatt: J. Lab. & Clin. Med. **24**: 337, 1939 Alpert: Arch. Pediat. **56**: 647, 1939 Feinblatt, Ferguson and Alpert: Endocrinology **26**: 437, 1940
A protein-free substance and insulin (neoinsulin)	Comparable in action to protamine zinc insulin	Lasch: Deutsche med. Wchnschr. **65**: 1154, 1940
Chloroform-precipitated insulin	Similar in action to protamine zinc insulin	Johlin: Endocrinology **29**: 574, 1941

recent comparative study by Bailey and Marble [27] adequately described the detail of their action. Histone zinc insulin approximates in action that of protamine zinc insulin. The action of globin (zinc) insulin, a soluble preparation, reaches its point of maximum intensity six to twelve hours after injection and wanes appreciably within twenty-four hours. Thus, there is usually no need to supplement its action to control the day feeding periods, and it is less likely to cause nocturnal insulin shock. In these respects it is comparable to some of the mixtures to be described

27. Bailey, C. C., and Marble, A.: Histone Zinc Insulin, Globin (Zinc) Insulin and Clear Protamine Zinc Insulin: A Comparative Study of Their Action, J. A. M. A. **118**:683-690 (Feb. 28) 1942.

later. It appears to be the most promising of all other insulins with intermediate effects.

Acid protamine zinc insulin, a soluble preparation derived from ordinary protamine zinc insulin by acidification to a p_H of about 3.3, possesses an intermediate action similar to that described for globin insulin. However, according to Bailey and Marble, its action is quantitatively inconsistent from dose to dose, possibly because it owes its intermediate effect to partial reprecipitation of protamine zinc insulin by tissue fluids after injection, resulting in variable rates of absorption of uncertain soluble and insoluble fractions.[28] Its action, like that of globin insulin, cannot be varied to suit individual requirements in treatment, an advantage which is inherent in the mixtures to be reported.

DETAILED INVESTIGATION OF THE ACTION OF MIXTURES

The need for a preparation which might combine the advantages and eliminate the disadvantages of both standard insulins is amply demonstrated by previous work with mixtures and the extensive search for other suitable insulin combinations. None of them has gained widespread popularity in practice, possibly because none fulfils requirements which are exacting or possibly because simplicity in the treatment of diabetes is highly desirable.[27]

Yet in the treatment of severe diabetes requiring multiple injections there is real need for a preparation with an action intermediate between that of soluble insulin and that of protamine zinc insulin. Hence, the action of mixtures was investigated by means of a method which shows accurately various changes in promptness, intensity and duration of hypoglycemic effects. The results show that (1) regular insulin in sufficient quantity added to protamine zinc insulin is reflected by increasing promptness and intensity of the sugar-reducing response; (2) the response depends on the proportion of insulin added, but only beyond a certain limit; (3) such mixtures are relatively stable, and (4) the response is uniform in a given patient and therefore predictable within the limits of error involved in any form of insulin therapy. A suitable mixture of the two standard insulins can be more efficient for routine use in the treatment of diabetes than either of the elements of which it is composed, as well as more simple and more consistent in response than both injected separately. Multiple injections of soluble and of insoluble insulin may be avoided. These inferences appear to be justified by the responses of constant glycosuria and hyperglycemia in test patients to single doses of various mixtures of the two insulins.

28. Marble, A.: Personal communication to the authors.

METHOD AND MATERIAL

Subjects.—Three carefully selected patients with diabetes mellitus lived quietly in the hospital as test subjects. They were 66, 62 and 56 years old; 2 were women, and all were cooperative, emotionally stable, in normal nutrition and free from acute complications. None had used insulin routinely, and none had shown rapid change in severity of diabetes prior to the tests. Glycosuria and hyperglycemia of moderate and constant degree resulted from the diets outlined in this section; ketonuria and signs of dehydration were absent. These factors are important in well controlled experiments of this nature because all of them are capable of varying the quantitative results and hence affecting their interpretations.

Food Intake.—All subjects were fed every four hours, day and night, throughout the experimental periods. On the average their daily weighed intake was carbohydrate 240 Gm., protein 90 Gm. and fat 100 Gm., divided into six equally spaced four hour feedings of almost identical foods and food values. In all cases the measured glycosuria and hyperglycemia were permitted to become constant on each diet for several days before a dose of the insulin to be tested was given.

The amount of blood sugar and urinary sugar showed a uniform tendency to decrease during the afternoon and to increase during the night. These diurnal changes did not affect the twenty-four hour values. They are reflected in the minor fluctuations in the curves to be shown; they do not obscure the major results due to insulin, and they were partially corrected by slight increases in the noon, afternoon and early evening feedings over those of the night and early morning.

In each patient during the two or three months of observation under the conditions just outlined there was a gradual improvement in "tolerance" for ingested food, which resulted in a tendency for the sugar levels to fail to return to their former heights after insulin was given. On this account, the value of the diet was increased slightly on occasion in order to force the sugar to resume its former control levels. Whenever such an increase was made, several days of new control values comparable to those shown previously were obtained before new tests were conducted.

Insulin.—Ordinary insulin and protamine zinc insulin were used consistently.[29] One patient (fig. 2) received these two insulins and their mixtures in the U-40 strength only. The other 2 patients received U-80 insulin only. In some instances the two insulins were freshly mixed in the syringe at the time of injection; in others they were mixed in the ampule under sterile precautions and allowed to stand at room or at ice box temperature. No decided variation in effect could be observed with mixtures standing as long as forty-seven days at room temperature.

All injections were made subcutaneously before the 8 a. m. or the 12 noon feeding. All traces of insulin effect from the previous injection were allowed to disappear before a subsequent injection was made, a process usually requiring three to four days.

Blood and Urinary Sugar.—Blood was drawn from a vein immediately before a four hour feeding and analyzed by the method of Folin and Wu. The urine of the first patient was collected in four hour specimens after each meal (figs. 1 and 2) and that of the other 2 patients in twelve hour specimens from 8 a. m. to 8 p. m. and 8 p. m. to 8 a. m. (figs. 3 and 4). Urine was analyzed for sugar by the method of Folin and Berglund.

29. Dr. F. B. Peck and Eli Lilly and Company furnished both types of insulin.

RESULTS

Control Values Without Insulin.—Without insulin the concentration of sugar in the blood and the amount in the urine were fairly constant at the levels of about 250 to 300 mg. per hundred cubic centimeters of blood and 10 to 20 Gm. per twelve hours in the urine (or 2 to 8 Gm. per four hours). These levels were uniform for all 3 patients (tables 2, 3 and 4 and figs. 2*A*, 3*A* and 4*A*). Since the diets prescribed were of the same order of magnitude in all cases, this uniformity indicates comparable severity of diabetes in all 3 patients, suggested further by their consistent responses to similar doses of insulin. Thus the results are peculiarly comparable, not only from dose to dose in the same patient but from patient to patient with the same dose.

As a side issue it is of interest to note the normal diurnal variations in observed levels of sugar in the blood and in the urine without insulin. Invariably, sugar tended to diminish during the day, reaching its lowest

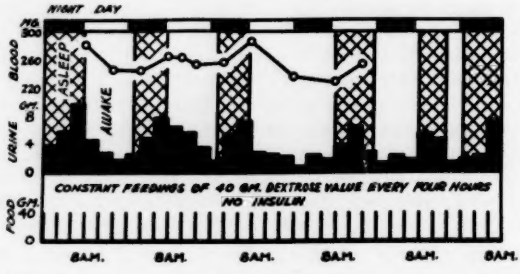

Fig. 1 (patient 1).—Diurnal variations in the levels of blood sugar and urinary sugar despite four hour feedings of constant value. Note the increases during sleep and the decreases during activity, even though the patient slept during the day and was awake at night. No insulin was given.

levels in the late afternoon, followed by increasing levels during the night, which reached their peaks, as a rule, in the early morning hours. This behavior is illustrated typically in the first patient (fig. 1), who after four hour meals of comparable value excreted as little as 2 Gm. of sugar per four hours in the afternoon and as much as 9 Gm. per four hours between 4 and 8 a. m. The concentrations of blood sugar varied in the same directions but to a smaller degree.

On the assumption that these fluctuations, the exact reverse of the well known diurnal variations in body temperature and total metabolism, are normal responses to exercise and activity during waking hours and to retardation of metabolic functions during sleep, this patient's hours of sleep and waking were reversed. For several days she was kept

awake at night and allowed to sleep during the day. The peaks and valleys of sugar excretion and of concentration of sugar in the blood were correspondingly reversed, as shown in the latter part of fig. 1. Thus they proved to be related to activity when awake and inactivity when asleep rather than to specific portions of the day. They could not be related to food, since the feedings were constant day and night.

Comment.—Similar observations are on record in the German and the Scandinavian literature.[30] They are not well known in this country. These fluctuations undoubtedly affect the behavior of persons with diabetes with and without insulin and should be respected in planning details of diet and insulin control. In our experience they affect the hour by hour performance of sugar metabolism more profoundly than certain details of timing and quantity of food and insulin which are often stressed in discussions of rules of treatment.

This tendency toward reduction of sugar during the day and increase at night may also affect the responses of normal and of diabetic subjects to standard dextrose tolerance tests. Since such tests are usually performed in the morning, recovery from hyperglycemia may depend as much on a natural tendency for sugar to diminish with activity during the day as to stimulation of insulinogenic function by ingested dextrose. This would be particularly true of the Exton-Rose two dose test.[31]

Commonly accepted interpretations of the Staub-Traugott,[32] or Hamman-Hirschman,[33] phenomenon might be subject to revision by a consideration of the facts just outlined. This phenomenon consists of successive lower hyperglycemic responses to repeated identical doses of ingested dextrose. It is considered to demonstrate an increased capacity to utilize sugar resulting from stimulation of the pancreatic islands by previous doses.[34] Our observations confirm this behavior during the

30. Hopmann, R., and Martini, H.: Der Tag-Nachtrhythmus des Diabetes mellitus, Ztschr. f. klin. Med. **129**:70-80, 1935. Vesa, A.: Studien über Diabetes Mellitus, Acta med. Scandinav., 1934, supp. 57, pp. 1-201.

31. Mathews, M. W.; Magath, T. B., and Berkson, J.: The One Hour–Two Dose Dextrose Tolerance Test (Exton-Rose Procedure), J. A. M. A. **113**:1531-1537 (Oct. 21) 1939.

32. Staub, H.: Untersuchungen über den Zuckerstoffwechsel des Menschen, Ztschr. f. klin. Med. **93**:89-140, 1922. Traugott, K.: Ueber das Verhalten des Blutzuckerspiegels bei wiederholter und verschiedener Art enteraler Zuckerzufuhr und dessen Bedeutung für die Leberfunktion, Klin. Wchnschr. **1**:892-894 (April 29) 1922.

33. Hamman, L., and Hirschman, J. J.: Studies on Blood Sugar: Effects upon Blood Sugar of Repeated Ingestion of Glucose, Bull. Johns Hopkins Hosp. **30**: 306-308 (Oct.) 1919.

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day, but since repeated identical feedings during the sleeping hours lead to the opposite, a tendency for sugar to increase, it seems possible that the Staub-Traugott phenomenon is due to a diurnal variation in sugar utilization which occurs as a result of physical activity rather than to stimulation of insulinogenic function by ingested carbohydrate, as commonly supposed. Otherwise, it would also occur during hours of sleep.

TABLE 2.—*Effect on the Concentrations of Blood Sugar and Urinary Sugar of Forty Unit and Eighty Unit Doses of U-40 Insulins and Insulin Mixtures* *

	No Insulin		Protamine Zinc Insulin		33% PZI 67% I †		25% PZI 75% I ‡		20% PZI 80% I		Regular Insulin	
Hour	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.
8 a.m.	290	....	288	...	281	...	242	...	247	...	281	...
4 p.m.	...	....	...	...	...	...	...	...	...	...	245	...
8 p.m.	...	13.3	...	...	...	...	...	...	...	...	...	...
12 midnight	...	....	...	...	...	...	...	...	...	...	245	...
4 a.m.	...	....	...	...	...	...	...	...	...	...	...	...
8 a.m.	281	19.7	272	...	251	...	269	...	260	...	265	...
12 noon	...	....	267	5.6	230	4.6	252	4.0	234	4.4	250	4.2
Insulin	None		80 units		80 units		80 units		80 units		40 units	
4 p.m.	245	....	204	4.2	208	3.1	131	1.8	162	2.2	116	0.7
8 p.m.	...	8.8	194	0.7	179	1.3	89	0.1	77	0.1	170	0.1
12 midnight	245	....	183	0.1	170	0.2	117	0.1	112	0.1	208	0.9
4 a.m.	...	....	...	0.1	...	0.2	...	0.1	...	0.1	...	3.4
8 a.m.	265	15.0	204	1.4	163	0.5	212	2.0	197	0.9	250	7.2
12 noon	263	....	185	0.4	180	0.7	237	2.5	225	2.7	263	6.4
4 p.m.	251	....	...	0.4	185	0.8	198	2.0	218	2.9	251	5.0
8 p.m.	...	14.7	212	0.5	211	0.6	228	1.7	...	3.9	...	3.3
12 midnight	256	....	...	1.2	224	0.8	201	1.4	246	2.4	256	1.3
4 a.m.	...	....	...	4.4	...	3.5	...	2.9	...	6.2	...	5.4
8 a.m.	288	14.1	281	6.2	249	5.0	237	4.5	236	7.4	288	7.4
12 noon	...	....	...	...	...	...	...	...	225	5.3	...	...
8 a.m.	270	13.8	267	4.7	285	3.5	262	4.1	...	...	272	6.0

* Patient 1, a 66 year old woman with diabetes of three years' duration. She had not taken insulin previously. Feedings were given every four hours, night and day, with an average dextrose value of 40 Gm.

† Averages for two identical doses. Here and elsewhere in the table PZI refers to protamine zinc insulin and I to regular insulin.

‡ Averages for four identical doses.

These diurnal fluctuations in glycosuria and hyperglycemia in spite of constant feedings were appreciable in all patients studied. They raised the early morning and lowered the afternoon sugar levels slightly. They were obviously not of sufficient magnitude to obscure the major responses to large doses of insulin.

Responses to Soluble Insulin and to Protamine Zinc Insulin.—Tables 2, 3 and 4 and figures 2 *F*, 3 *F* and 4 *D* show typical sugar-reducing effects of 40, 80 and 80 unit doses, respectively, of ordinary soluble insulin. Familiar peak effects at about four hours after injection

TABLE 3.—*Effect on the Concentrations of Blood Sugar and Urinary Sugar of Eighty Unit Doses of U-80 Insulins and Insulin Mixtures**

	No Insulin		Protamine Zinc Insulin		50% PZI 50% I †		33% PZI 67% I ‡		25% PZI 75% I		Regular Insulin	
Hour	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.
8 a.m.	...	....	261	....	255	....	282	....	276	....	310	....
4 p.m.	261	....	...	....	...	....	286	....	...	....	...	....
8 p.m.	...	8.7	...	9.2	239	15.0	...	19.1	...	17.8	...	17.9
12 midnight	305	....	...	....	...	....	301	....	...	....	...	....
8 a.m.	310	16.5	284	9.7	250	7.3	292	12.5	276	9.5	284	19.3
Insulin	None		80 units		80 units		80 units		80 units		80 units	
12 noon	...	....	...	....	253	....	242	....	162	....	61	....
4 p.m.	...	....	248	....	204	....	193	....	82	....	132	....
8 p.m.	...	11.2	247	7.0	183	7.8	161	6.1	83	0.8	245	1.5
12 midnight	...	....	235	....	149	....	153	....	87	....	230	....
8 a.m.	302	11.5	206	2.3	126	0.5	181	0.2	175	0.3	292	7.0
4 p.m.	...	....	187	....	183	....	215	....	235	....	263	....
8 p.m.	...	9.4	...	0.5	...	2.9	...	3.9	...	5.3	...	....
12 midnight	288	....	217	....	219	....	224	....	230	....	...	....
8 a.m.	286	14.8	253	1.4	242	10.1	252	5.1	250	5.1	250	21.0
8 p.m.	315	14.7	242	2.8	235	....	249	9.3	230	....	315	....
8 a.m.	312	12.0	274	4.0	247	11.5	250	4.3	229	8.2	294	21.5
8 p.m.	301	12.3	...	5.0	231	....	...	11.0	...	....	...	....
8 a.m.	312	10.4	298	4.0	244	10.3	269	7.4	258	7.7	...	....

* Patient 2, a 62 year old woman with diabetes of one year's duration. She had not taken insulin previously. Feedings were given every four hours, night and day, with an average dextrose value of 45 Gm.

† Throughout the table PZI refers to protamine zinc insulin and I to regular insulin.

‡ Averages for four identical doses.

TABLE 4.—*Effect on the Concentrations of Blood Sugar and Urinary Sugar of Eighty Unit Doses of U-80 Insulins and an Insulin Mixture**

	No Insulin		Protamine Zinc Insulin		25% PZI 75% I †		Regular Insulin †	
Hour	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.
8 a.m.	266	....	238	....	272	....	280	....
8 p.m.	...	....	248	19.2	227	13.8	256	18.6
8 a.m.	274	16.7	242	15.7	277	18.5	270	16.4
Insulin	None		80 units		80 units		80 units	
12 noon	...	....	213	....	71	....	63	....
4 p.m.	...	....	196	....	75	....	123	....
8 p.m.	...	....	178	11.2	85	3.1	236	1.9
12 midnight	...	....	190	....	90	....	228	....
8 a.m.	283	15.8	206	7.0	157	0.3	277	13.1
4 p.m.	...	....	184	....	205	....	252	....
8 p.m.	256	....	...	5.5	...	3.3	242	18.1
12 midnight	...	....	205	....	213	....	...	....
8 a.m.	286	17.6	200	6.3	256	11.1	275	17.1
8 p.m.	256	....	248	15.0	...	9.4	216	17.2
8 a.m.	286	17.8	242	19.0	269	11.2	255	13.3

* Patient 3, a 56 year old man with diabetes of 12 years' duration. He had not taken insulin previously. Feedings were given every four hours, night and day, with an average dextrose value of 56 Gm.

† Averages for two identical doses. PZI refers to protamine zinc insulin and I to regular insulin.

and return to control levels within twenty-four hours are apparent, accompanied by substantial reduction of glycosuria for twelve to twenty-four hours.

Figures 2 *B*, 3 *B* and 4 *B* and tables 2, 3 and 4 illustrate typical responses to 80 unit doses of protamine zinc insulin, with signs of maximum intensity at twenty-four to thirty-two hours after administration and associated gradual and prolonged reduction of glycosuria for at least two days.

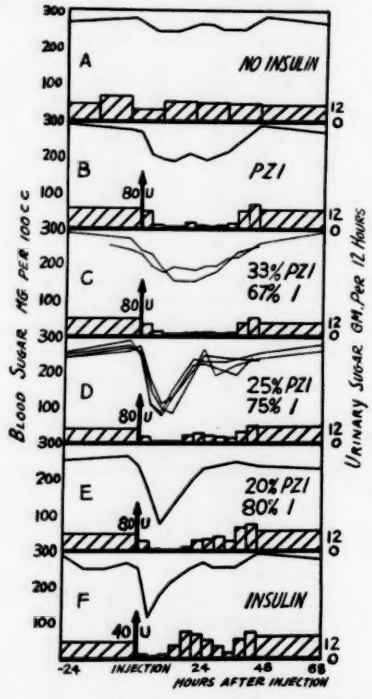

Fig. 2 (patient 1).—A graphic record of the values in table 2. *A*, no insulin was given. *B*, the response to protamine zinc insulin (*PZI*). *C*, *D* and *E*, intermediate responses to mixtures containing increasing proportions of ordinary insulin (*I*). Superimposed curves represent the responses to repeated identical doses. *F*, the response to ordinary insulin. Contrast this with the response to protamine zinc insulin (*B*).

Comment.—Although these data illustrate the pharmacologic reactions to the two standard insulins in doses somewhat larger than those commonly used in routine treatment, their characteristic time relations and comparable intensity and duration of reaction vividly illustrate the

difficulties inherent in treatment with one or both of them in cases of severe diabetes in which large doses are required. The prompt, brief action of ordinary insulin causes violent hypoglycemia and permits heavy glycosuria and acidosis unless it is given at frequent intervals. The weak, sustained action of protamine zinc insulin permits glycosuria after meals and tends to cause nocturnal hypoglycemia during fasting.[35] Hence a single insulin with an intermediate action is highly desirable.

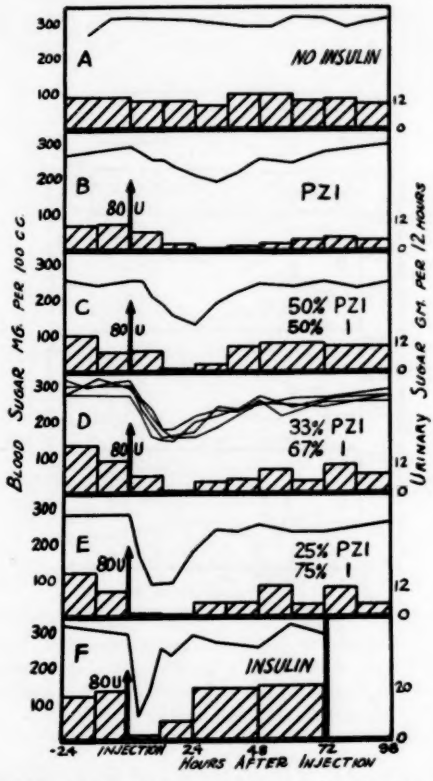

Fig. 3 (patient 2).—A graphic record of the values in table 3. *A*, no insulin was given. *B*, the response to protamine zinc insulin (*PZI*). *C*, *D* and *E*, intermediate responses to mixtures containing increasing proportions of ordinary insulin (*I*). Note the similarity between the curves in *C* and *B*. The superimposed curves in *D* represent responses to repeated identical doses, two of which were mixed several weeks before injection. *F*, the response to ordinary insulin. Contrast this with the response to protamine zinc insulin (*B*).

35. Footnotes 4 and 5.

Response to Mixtures.—The comparative effects of various mixtures of the two insulins are graphically illustrated in figures 2 *C*, *D* and *E*; 3 *C*, *D* and *E*, and 4 *C*. Tables 2, 3 and 4 present the actual values obtained. In effect a mixture containing equal proportions of the two insulins (fig. 3 *C*) is barely distinguishable from protamine zinc insulin; a mixture containing four parts soluble insulin and one part protamine zinc insulin (fig. 2 *E*) resembles ordinary insulin, but the action of the latter mixture reaches its peak about twice as late and recedes more slowly. Intermediate mixtures containing two and three parts of soluble insulin to one part protamine zinc insulin show inter-

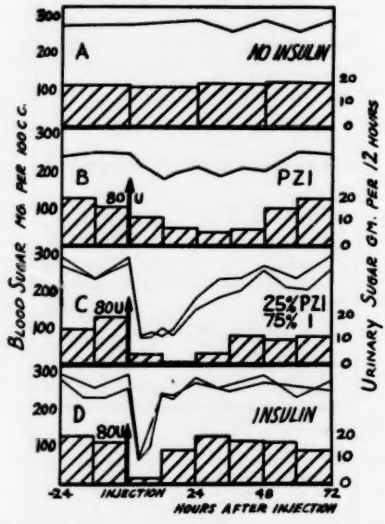

Fig. 4 (patient 3).—A graphic record of the values in table 4. *A*, no insulin was given. *B*, the response to protamine zinc insulin (*PZI*). *C*, intermediate responses to a 3:1 mixture of regular insulin (*I*) and protamine zinc insulin after duplicate identical doses. *D*, the response to ordinary insulin. Contrast this with the response to protamine zinc insulin (*B*).

mediate actions (figs. 2 *C*, 2 *D*, 3 *D*, 3 *E* and 4 *C*). With characteristic peak effects at eight to sixteen hours, contrasting with four hours for soluble insulin and twenty-four hours or later with protamine zinc insulin; intensity intermediate between the other two, and definite waning effects at twenty-four hours, these mixtures clearly possess pharmacologic properties intermediate between those of insulin and of protamine zinc insulin. In these respects the mixtures all run in series from one extreme to the other.

The characteristic reactions of identical doses of these insulins and their mixtures in various proportions appeared uniform enough in the 3 test subjects to justify a composite graph and diagrammatic deduction as to their actions. Figure 5 *A* shows four mean curves obtained by computing averages for all tests with 80 unit doses of the two insulins and two of their mixtures. In figure 5 *B* these curves are smoothed out in diagrammatic fashion. The smoothing process is intended arbitrarily to eliminate or discount obvious irregularities caused by diurnal variations due to activity and sleep rather than to insulin.

Composite curves obtained in this manner show clearly the familiar blood sugar–reducing effects of large doses of regular insulin and of

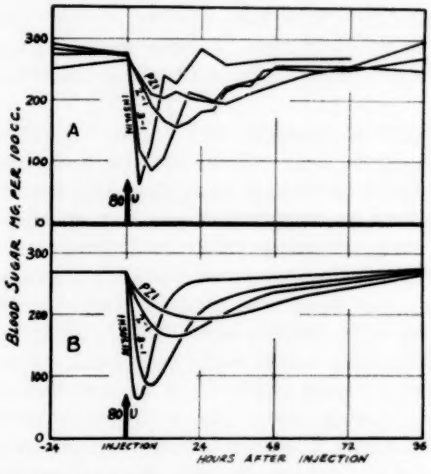

Fig. 5.—*A*, average blood sugar curves for all identical doses of similar insulins or insulin mixtures in all patients (*PZI*, protamine zinc insulin; *2-1*, a mixture containing two parts regular insulin to one part protamine zinc insulin, and *3-1*, a mixture containing three parts regular insulin to 1 part protamine zinc insulin). *B*, diagrammatic representation of the average curves shown in *A*, arbitrarily smoothed to discount minor irregularities considered not to be due to insulin.

protamine zinc insulin. Their characteristic forms establish confidence in the accuracy of the method of study. The curves illustrating the effects of the two most frequently studied mixtures are clearly intermediate between those of the two standard types of insulin. They show increasing promptness and intensity of action associated with more rapid waning as excesses of soluble insulin are added to the mixtures. Other single curves not included in the composite group fit into this scheme. All of them confirm the observations of Ulrich that little acceleration of

effect is obtained until at least as much regular insulin as protamine zinc insulin is used in the mixtures.[19]

Therefore, it is possible to conclude that mixtures of ordinary insulin and protamine zinc insulin in the U-40 or U-80 strengths used in this study can be combined empirically in mixtures containing at least as much of the former as the latter, with increasing acceleration and diminishing duration of effect in a consistent and graduated series as more soluble insulin is added.

Comment.—The intermediate modifications containing 67 and 75 per cent soluble insulin consistently show peaks of sugar-reducing activity eight to sixteen hours after injection, which would correspond to late afternoon and evening if daily morning injections were given. The effects tend to wane within twenty-four hours after injection, which would correspond to the night hours of fasting with daily morning injections. Both features appear desirable from the standpoint of clinical usefulness.

However, when one considers the possible clinical use of such modifications, it must be remembered that the promptness, intensity and duration of effect described for them occur under conditions which are different from those existing in practice. First, the doses illustrated are larger than those generally used daily by diabetic patients. Second, in these experiments the blood sugar and urinary sugar decrease from levels much higher than those existing in patients with well controlled diabetes at the time of insulin injection. Third, the subjects reported ate generous carbohydrate meals every four hours, even during the night. Finally, the reactions of the 3 test subjects described may not be average for all diabetic patients. Hence, clinical applications of these actions of specific mixtures must be made with extreme caution and with full consciousness of the different conditions in routine treatment from those reported here. Our own experience in this respect is reported in the following section.

Questions concerning the consistency of repeated injections of the same preparations are answered by figures 2 *C*, 2 *D*, 3 *D* and 4 *C*. These curves show the blood sugar responses to two and to four identical doses of the same mixture in the same subject. The response appears to be fairly dependable and predictable, as noted by Ulrich, using other methods. Complete uniformity of response would be a desirable property of any relatively slow-acting insulin. Certainly one of the chief disadvantages of protamine zinc insulin is its tendency to permit undulating variations in control from day to day.

The modifications described apparently are stable for weeks, at least. In figure 3 *D* two of the four superimposed blood sugar curves followed

injection of mixtures which were freshly prepared. The other two followed identical doses of similar mixtures prepared in an ampule and allowed to stand at room temperature for thirty and forty-seven days.

NATURE OF THE MODIFIED INSULIN

In addition to precipitated insulin, water and preservative, protamine zinc insulin contains protamine (much of it uncombined), zinc and dibasic sodium acid phosphate. Of these last-named three ingredients, ordinary insulin contains only zinc in about one-tenth the quantity present in protamine zinc insulin. Therefore, on an empiric basis mixtures like those reported should contain less than half the quantity of all three substances in proportion to their insulin content. Which of these ingredients in reduced concentration is responsible for the accelerated action is not known. Theoretically, less of any one of them would be capable of accelerating the slow action of protamine zinc insulin.

The addition of zinc certainly prolongs the action of protamine insulin. How much less than 0.2 mg. of zinc per hundred units would be required to modify the effect is not known. There is also evidence that increased acidity and reduced protamine both modify the action of protamine zinc insulin in the direction shown by the mixtures. We have reason to believe that reduced protamine is the major cause for the accelerated action but that increased acidity and less zinc are also capable of modifying the action in the same manner. Which of the two last-named factors is more important is speculative.

As noted by Ulrich, the modified insulin action exhibited by these mixtures is probably not due to soluble insulin in them.[19] We have confirmed his observation that the supernatant liquid from a centrifuged mixture containing three parts soluble insulin and one part protamine zinc insulin is essentially free from insulin effect. Therefore, the insulin in the mixture must be in precipitated form, possibly adsorbed on the protamine zinc insulin precipitate or possibly in the form of a more freely soluble protamine insulinate than that existing in the presence of more protamine and in the more alkaline suspension. Further studies on the nature of the modified insulin are in progress and will be reported.

THERAPEUTIC EXPERIENCE

Practical application of the mixtures just described has been deliberately restricted to careful observation of a few selected patients. Twelve patients, most of them with severe diabetes of the juvenile type, have used mixtures containing 60 to 75 per cent ordinary insulin and 40 to 25 per cent protamine zinc insulin in single daily doses (in 1 instance twice daily) for periods up to six months. Nine patients had used

protamine zinc insulin with supplementary injections of soluble insulin previously, causing irregularly imperfect control. They had been unable to avoid waves of heavy glycosuria under the best possible conditions with weighed diets and separate injections. Hypoglycemic symptoms had been frequent and unpredictable.

In 8 of these 9 patients the severe diabetes is under decidedly better control with a single daily dose of a 2 to 1 or 3 to 1 mixture than with a single daily dose of protamine zinc insulin supplemented by one or two small daily doses of soluble insulin. One patient reverted to separate injections after a three week trial on a 3 to 1 mixture. In this instance an infection of the respiratory tract during the period of trial probably vitiated the results. In the other 3 patients the diabetes was capable of good control with protamine zinc insulin alone; the control is fully as good with a mixture of two or three parts soluble insulin and one part protamine zinc insulin.

The chief difficulty encountered so far has been a tendency to hypoglycemia at the hour when it would be anticipated, i. e., in the late afternoon, at the point of coincidence of the greatest activity of the day with the peak of the insulin action. In some instances reduction of the total dose or increases in the noon meal and insertion of a midafternoon feeding have been sufficient to prevent hypoglycemic symptoms without increases in glycosuria elsewhere. In other cases mixtures containing less soluble insulin may be preferable. They have not yet been tried. In practically all cases a substantial reduction in dose has been necessary when mixtures were used.

SUMMARY

Responses of constant hyperglycemia and glycosuria to single doses of insulin, protamine zinc insulin or simple mixtures of the two in various proportions justify the following conclusions:

1. Suitable mixtures of the two standard insulins may be prepared which show any desired intermediate action between the two in promptness, intensity and duration of effect.

2. Such intermediate effects gain intensity and promptness at the expense of prolongation of action. The converse is also true.

3. Intermediate effects which are decisive cannot be obtained with simple mixtures of the two insulins until as much soluble insulin as protamine zinc insulin is used in them.

4. Probably mixtures containing more regular insulin than protamine zinc insulin, possibly two or three times as much, are most suitable for daily use in the treatment of severe diabetes.

5. Such mixtures owe their intermediate effects to reduction in the amount of protamine, zinc or alkaline buffer. There is evidence to

indicate that insulin in a different physical or chemical form is responsible for the modified action rather than composite effects from simple fractions of soluble insulin and insoluble protamine zinc insulin.

6. Results of treatment with these modifications suggest that better control of severe diabetes mellitus may be obtained with single daily doses of one of them than with protamine zinc insulin or unmodified insulin given alone or both administered simultaneously in separate doses. Multiple injections may be avoided and dosage reduced because of greater efficiency.

636 Church Street.

DISTRIBUTION OF SPECIFIC TYPES OF HEMOLYTIC STREPTOCOCCI IN EIGHT HUNDRED AND NINETEEN CASES OF INFECTION

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In two previous papers by two of us (L. A. R. and C. S. K.) and an associate [1] it was pointed out that hemolytic streptococci of groups A, B and C can be readily distinguished by the specific precipitin method of Lancefield [2] and that they also give distinctive types of hemolysis in standard poured blood agar plates.[1a] Group A hemolytic streptococci are made up of a number of specific types, which may be distinguished by appropriate serologic methods.[3] For this purpose two procedures have been used, (1) the slide agglutination method of Griffith [4] and (2) the precipitin method of Lancefield.[2] Of the two, the slide agglutination method has had wider use. Most of the reports concerning the distribution of specific types of hemolytic streptococci in human disease have

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) and the South Department, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. (*a*) Rantz, L. A., and Jewell, M. L.: The Relationship of Serologic Groups A, B, and C of Lancefield to the Type of Hemolysis Produced by Streptococci in Poured Blood Agar Plates, J. Bact. **40**:1, 1940. (b) Rantz, L. A., and Keefer, C. S.: The Distribution of Hemolytic Streptococci Groups A, B, and C in Human Infections, J. Infect. Dis. **68**:128, 1941.

2. Lancefield, R. C.: Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571, 1933.

3. Lancefield, R. C.: Antigenic Complex of Streptococcus Hemolyticus: Demonstration of Type-Specific Substance in Extracts of Streptococcus Haemolyticus, J. Exper. Med. **47**:91, 1928.

4. Griffith, F.: (*a*) The Serological Classification of Streptococcus Pyogenes, J. Hyg. **34**:542, 1935. (*b*) Types of Haemolytic Streptococci in Relation to Scarlet Fever, ibid. **25**:385, 1926.

been made from England [5] and Australia,[6] but a few have appeared from Japan,[7] Germany [8] and the United States.[9] In 1938 and 1939 we were able to study 819 strains of group A hemolytic streptococci by the slide

5. (*a*) Griffith, F.: Types of Haemolytic Streptococci in Relation to Scarlet Fever, J. Hyg. **26**:363, 1927. (*b*) Smith, J.: The Serological Classification of Haemolytic Streptococci Obtained from Cases of Scarlet Fever, ibid. **25**:165, 1926. (*c*) Further Studies on the Serological Classification of Haemolytic Streptococci, ibid **26**:420, 1927. (*d*) Gunn, W., and Griffith, F.: Bacteriological and Clinical Study of One Hundred Cases of Scarlet Fever, ibid. **28**:250, 1928. (*e*) Green, C. A.: Serological Types of Haemolytic Streptococci in an Epidemic of Scarlatina, ibid. **37**:318, 1937. (*f*) de Waal, H. L.: Serological Types of Haemolytic Streptococci in Relation to the Epidemiology of Scarlet Fever and Its Complications, ibid. **40**:172, 1940. (*g*) Cooke, M. J., and Neisser, H.: Serological Types of Streptococcus Pyogenes in Scarlet Fever, Ann. Rep. London County Council **4**:104, 1937. (*h*) Neisser, H.: Serological Typing of Streptococcus Pyogenes and Its Applications to Certain Infective Conditions, J. Path. & Bact. **8**:55, 1939. (*i*) de Waal, H. L.: A Study of the Serological Types of Haemolytic Streptococci in Relation to the Epidemiology of Scarlatina and Other Infections Due to These Organisms, J. Hyg. **41**:65, 1941. (*j*) Brown, W. A., and Allison, V. D.: Carriers and Return Cases in Scarlet Fever, ibid. **35**:283, 1935. (*k*) Allison, V. D., and Gunn, W.: Epidemiology of Streptococcal Infections, Proc. Roy. Soc. Med. **25**:927, 1932. (*l*) Griffith.[4b]

6. (*a*) Butler, H. M., and Hill, A. M.: Haemolytic Streptococcal Infections Following Childbirth and Abortion: I. Determination of Virulence of Group A Strains, M. J. Australia **1**:222, 1940. (*b*) White, C.; Rudd, G. V., and Ward, H. K.: Serological Types of Haemolytic Streptococci Causing Scarlet Fever in Sydney, ibid. **1**:96, 1939. (*c*) Keogh, E. V.; MacDonald, I.; Battle, J.; Simmons, R. T., and Williams, S.: Some Factors Influencing the Spread of Scarlet Fever in an Institution, J. Hyg. **39**:664, 1939. (*d*) Keogh, E. V.; MacDonald, I.; Battle, J.; Simmons, R. T., and Puckey, M. C.: Serological Types of Streptococci Associated with Scarlet Fever in Adelaide, M. J. Australia **1**:792, 1939.

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agglutination technic. The rabbit serum for this investigation was made by using subcultures of the original Griffith strains. The purpose of the study was to determine the types of streptococci which were prevalent those years and to ascertain whether any information concerning the severity of infection, complications and other features of the infections could be related to specific types.

MATERIAL AND METHOD

Cultures were made of material from various foci of infection in poured blood agar plates, and beta hemolytic streptococci were isolated. They were first identified as to group, according to the microprecipitin method of Brown.[10] Strains which proved to belong in group A were then set up for typing. The slide agglutination method of Griffith [4a] was used. The organisms were grown in various kinds of medium in an attempt to obtain stable and even suspensions. We found that the growth of organisms in trypsin broth was satisfactory for most strains, since the

TABLE 1.—*Foci of Infection from Which Hemolytic Streptococci Were Isolated*

	Number of Strains	Percentage
Throat infections	531	64.0
Otitis media and mastoiditis	120	14.0
Abscesses (miscellaneous)	58	7.0
Pneumonia and empyema	57	7.0
Bacteremia	37	4.7
Erysipelas	12	1.6
Meningitis	4	0.5
Total	819	

suspensions were more likely to be nongranular in this medium. When the cultures were granular, it was not possible to use them for typing. The serums were absorbed, so that cross reactions were eliminated. The sources of the organisms are shown in table 1.

DISTRIBUTION OF TYPES OF HEMOLYTIC STREPTOCOCCI IN VARIOUS DISEASES

The distribution of the various types of hemolytic streptococci in different diseases is shown in table 2. Six hundred and thirty-seven, or 79 per cent, of the 819 strains were typed with the serums that were available. The frequency with which we identified these types ranged from 61 to 83 per cent in the various diseases. In the cases of pneumonia and tonsillitis, we identified 61 and 65 per cent of the strains, respectively, whereas in the cases of scarlet fever, otitis media and mastoiditis 83 per cent of the strains were typed. It has been recognized by

10. Brown, J. H.: A Simplified Method for Grouping Hemolytic Streptococci by the Precipitin Reaction, J. A. M. A. **111**:310 (July 23) 1938.

every one who has attempted to identify types of hemolytic streptococci that it is more difficult to type strains which are isolated from persons with puerperal sepsis[11] or the throats of carriers than it is to identify those which are isolated from the throats of patients with scarlet fever. This is probably due to the fact that there are many types other than the ones originally isolated by Griffith which have not been identified and properly classified.

It is seen from table 1 that in cases of otitis media, mastoiditis, pneumonia, abscess and erysipelas which were studied during the same

TABLE 2.—*Distribution of Types of Causative Hemolytic Streptococci in Various Diseases*

Type	Scarlet Fever	Tonsillitis	Otitis Media and Mastoiditis	Abscess	Pneumonia	Empyema	Bacteremia	Erysipelas	Meningitis	Total
1	20	6	13	5	3	..	3	2	..	52
2	20	..	3	..	4	..	..	..	..	27
5	2	..	..	..	..	..	..	..	..	2
6	1	1	1	..	..	..	..	..	..	3
8	2	..	3	..	..	..	..	..	..	5
9	1	..	..	1	1	..	..	..	..	3
10	4	..	..	1	..	..	..	..	..	5
11	23	18	15	12	..	..	6	2	..	76
12	5	1	8	3	1	2	2	1	1	24
13	101	7	16	5	4	3	2	..	..	138
14	1	..	..	..	..	..	..	..	..	1
15	151	27	25	5	11	6	15	1	1	242
19	1	..	..	..	..	..	..	..	..	1
21	1	..	..	..	..	..	..	..	..	1
25	3	6	10	3	..	..	2	..	..	24
26	..	1	..	..	..	..	..	..	..	1
27	2	7	4	4	1	..	2	2	..	22
28	1	2	1	4	..	..	..	1	1	9
29	2	..	..	..	..	..	..	..	..	2
Typing unsuccessful	73	41	21	15	16	5	5	3	1	180
Total	414	117	120	58	41	16	57	12	4	819
Per cent of total no. of strains typed	83	65	83	74	61	69	70	75	75	79

period the infections were due to the same types of organism which were causing scarlet fever and tonsillitis. Another fact was noticeable; namely, when one type was most prevalent in patients with scarlet fever, it was also prevailing in those with other infections caused by hemolytic streptococci.

Scarlet Fever.—Of the 414 strains isolated from the throats of patients with scarlet fever, we were able to type 83 per cent of the

11. (*a*) Colebrook, D. C.: The Source of Infection in Puerperal Fever Due to Hemolytic Streptococci, Medical Research Council, Special Report Series, no. 205, London, His Majesty's Stationery Office, 1935. (*b*) Footnote 5 *h* and *i*. (*c*) Butler and Hill.[6a]

strains, and 75 per cent of them were found to fall into the following five types: 15, 13, 11, 1 and 2. When these results were compared with the typing of strains isolated from patients with tonsillitis, it was found that only 65 per cent of these strains could be typed, but the types which predominated were 15, 11, 13, 1, 25 and 27. There were no instances of tonsillitis due to hemolytic streptococci of type 2.

When the strains isolated from patients with scarlet fever and with tonsillitis were considered together, there were 531 strains and 79 per cent were typed. Seventy per cent of the strains fell into types 15, 13, 11, 1 and 2. The remaining 9 per cent were scattered among the other types. This is shown in table 3.

From these studies it is plain that the number of types responsible either for scarlet fever or for tonsillitis during the period of observation was relatively small, but the distribution of types was different from that reported elsewhere.

TABLE 3.—*Distributions of Types of Hemolytic Streptococci Isolated from Patients with Scarlet Fever and with Tonsillitis*

Type	Total No. of Strains	Percentage
15	178	33.0
13	108	20.0
11	41	7.7
1	26	4.8
2	20	3.9
		69.4

In the studies of the distribution of types of streptococci which cause scarlet fever in England and Scotland [12] it appears that while a large number of types are capable of causing scarlet fever, the commonest are types 1 to 5 inclusive, and they account for at least 60 per cent of all strains isolated. In a single study reported from Germany by Gundel and Wüstenberg [8] the same general distribution was found. In Australia, however, the distribution as reported by various investigators has varied from one community to another.[13] For example, in Sydney types 1, 4, 11 and 17 accounted for most of the streptococci causing scarlet fever. In Adelaide a type not included in Griffith's strains and called "Wade" strain was responsible for 55 of 78 infections, and in Melbourne type 2 predominated. According to a recent report from Scotland, types 1, 2, 4, 8, 11 and 15 predominated.[51] It is almost a universal experience that during an epidemic of scarlet fever one type of hemolytic streptococcus accounts for the majority of cases occurring in a community, and this

12. Footnote 5 *a* through *k*.

13. Footnote 6 *b*, *c* and *d*.

is especially striking when epidemics are studied in institutions. As an epidemic progresses in the same community, one specific type may be replaced by another. De Waal [51] described two epidemics of scarlet fever, occurring at the same time in communities 12 miles (19 kilometers) apart, which were due to different types.

In the United States Bailey [9c] found in 1934 and 1935 that types 2, 3 and 6 were the predominant types causing scarlet fever in Chicago. In New York city Pauli and Coburn [9b] and Coburn and O'Connell [9f] have shown that the predominating types in infections caused by hemolytic streptococci vary from year to year. In the years 1935 and 1936 types 4, 22 and 13 were common, and in 1937 and 1938 type 30 accounted for 35 per cent of the strains isolated and types 13, 15, 25, and 27 accounted for another 25 per cent of strains. They did not encounter one strain of type 10 in four years, although this strain (NY 5) was known to be prevalent for some years in and around New York city. The strains which were isolated in the early fall from cultures of material from the throats of healthy subjects frequently were difficult to type. Recently, Kuttner and Krumwiede [9e] reported their results of a study of pharyngitis caused by hemolytic streptococci in an institution over a three year period. During this time three different strains were isolated during epidemics of such pharyngitis, that is, a different strain every year. The first year it was C51, a group A strain which is not included in the 30 types identified by Griffith; the second year it was a strain of type 4, and the third, a strain of type 27. Other strains isolated at various periods included ones of types 2, 5, 6, 12, 17, 18 and 29.

Our own experience indicates, then, that during any one year the total number of strains which cause disease may be limited. During the period in which we studied the subject the predominating types were 15, 13, 11, 1 and 2, which accounted for 85.4 per cent of all the types identified.

From these various studies concerning the distribution of specific types of hemolytic streptococci which cause scarlet fever in different countries or in different communities of the same country the following facts emerge:

1. Scarlet fever may be caused by a wide variety of specific types of hemolytic streptococci.

2. The predominant types vary from one country to another, from one community to another in the same country and from year to year in the same country or community.

3. During an epidemic in a community, one type usually predominates or two types may thrive simultaneously. This is most noticeable when epidemics occur in schools or institutions.

4. As an epidemic progresses in the same community, one type may be replaced by another, so that the type which may be common at one season may be replaced by another type later.

5. In sporadic cases of scarlet fever the infections are more often due to types which are not concerned with the types causing the epidemic, and there is often a wide scattering.

6. When a relapse occurs in a patient with scarlet fever, it is usually because of infection by a different type of hemolytic streptococcus and because the patient's reaction to the Dick test has failed to become negative as a result of the first attack.

TABLE 4.—*Distribution of Types of Hemolytic Streptococci Causing Otitis Media and Mastoiditis in Patients With and Without Scarlet Fever*

Type	Total No. of Patients With Scarlet Fever	Patients With Otitis Media		Patients With Mastoiditis	
		With Scarlet Fever	Without Scarlet Fever	With Scarlet Fever	Without Scarlet Fever
15	151	9	16	0	4
13	101	12	4	0	1
11	23	1	14	0	10
1	20	4	9	0	3
2	20	1	2	0	0
12	5	2	6	0	3
25	3	0	10	0	3
10	4	0	0	0	0
5	2	0	0	0	0
8	2	1	2	0	1
27	2	0	4	0	1
29	2	0	0	0	0
6	1	1	0	0	0
9	1	0	0	0	0
14	1	0	0	0	0
19	1	0	0	0	0
21	1	0	0	0	0
28	1	0	1	0	1
Unidentified types	73	5	16	0	11

The relation of complications to type are discussed in a later section of the paper.

Otitis Media and Mastoiditis.—In this group there were 120 patients, 82 with otitis media alone and 38 with associated mastoiditis. That is to say, mastoiditis developed in 31 per cent of the patients with otitis media. Seventy-two per cent of the infections were accounted for by five different specific types: 15, 13, 11, 1 and 25. These were the types which were common in the throats of patients with scarlet fever and with tonsillitis during this period. The relative frequency of the different types causing otitis media and mastoiditis is listed in table 4. Also, in table 4 the relative frequency of otitis media and mastoiditis in patients with and in those without scarlet fever is recorded. The total incidence of otitis media in 414 patients with scarlet fever was 8.9 per cent. Since

the average incidence of otitis media following scarlet fever is about 12.5 per cent,[14] this is not an excessively high complicating rate in our series. When the causative organisms were analyzed for type, types 13, 9, 1 and the unidentified types were the most frequent cause of otitis media following scarlet fever. Types 11 and 15 and unidentified types caused most of the mastoiditis without preceding scarlet fever. Indeed, mastoiditis failed to develop in any of the 36 patients with otitis media following scarlet fever. This may have been due to treatment with sulfanilamide. Many of the patients who had mastoiditis without preceding scarlet fever were admitted to the hospital with well developed mastoiditis.

De Waal [51] reported otorrhea in 80 cases of scarlet fever, and types 4, 1 and 15 were common ones isolated in these cases.

In our patients mastoiditis occurred more often after otitis media without scarlet fever than with this disease. The incidence of this complication of otitis media may be reduced by using sulfanilamide regularly in all cases. Moreover, the occurrence of otitis media as a late complication of scarlet fever may be reduced either by preventing reinfection or by using sulfanilamide during the course of the disease.

Erysipelas.—In a previous study by one of us (C. S. K.) with an associate of 22 strains of hemolytic streptococci isolated from patients with erysipelas, it was found that they all belonged to group A and they did not differ from those obtained from patients with other infections.[15] In this study 12 strains were isolated, and 9 of them were typed, including types 1, 11, 12, 27 and 15. It was not surprising to find the same types in patients with erysipelas as were prevalent in persons with infections of the respiratory tract, since the same type of hemolytic streptococcus is frequently present in the nose and throat and in the cutaneous lesion. Indeed, there is good evidence that erysipelas of the face frequently follows infections of the nose and throat or infections of wounds caused by hemolytic streptococci. De Waal [51] has recently reported his results of typing hemolytic streptococci isolated in 40 cases of erysipelas; he found types 1, 2, 3, 4, 7, 25, 28 and 30 most often. It was of interest that he found type 7 in 6 cases, since this type belongs to group C Lancefield, and in our own experience we failed to isolate any organisms of this type from infections in human beings. A point of some interest was the fact that erysipelas in young persons, i. e., ones under 20 years

14. Abrams, J. I., and Friedman, S.: The Problem of Otitis Media and Mastoiditis in Scarlet Fever, New England J. Med. **209**:494, 1933. Wesselhoeft, C.: Factors Influencing the Incidence and Course of Otitis Media in Scarlet Fever, Ann. Int. Med. **12**:1473, 1939.

15. Keefer, C. S., and Spink, W. W.: Studies of Hemolytic Streptococcal Infection: III. The Characteristics of the Hemolytic Streptococci Isolated from Patients with Erysipelas, J. Clin. Investigation **16**:155, 1937.

of age, was associated with the types of hemolytic streptococci which were prevalent in the epidemic forms of this disease (types 1 to 4), whereas in the older patients the nonepidemic types prevailed. Also, in 1 case of recurrent erysipelas, the same type (type 7) was isolated on two different occasions. All of our patients with erysipelas recovered except 1 who had associated heart disease.

Pneumonia and Empyema Caused by Hemolytic Streptococci.—Forty-one patients had pneumonia and 16 had empyema caused by hemolytic streptococci. In the 41 patients with pneumonia, we were able to type 61 per cent of the causative strains of streptococci. In order of frequency, the types were 15, 13, 2, 1, 12, 9 and 27. The types which were associated with empyema were 15, 12 and 13. There was no correlation between the type of organism and the outcome, although the group was too small to draw definite conclusions. Empyema was more common in the patients under 30 years of age, and the fatality rate was correlated with age and the presence of bacteremia rather than with the type of infecting organism. That is, patients over 50 years of age and those with bacteremia have a poor prognosis. Those under 40 years of age without bacteremia frequently survive. It is well to point out that the organisms responsible for pneumonia were the same as those which were causing other infections. A full account of the cases of these patients has been published elsewhere,[16] but in order to stress certain facts about pneumonia caused by hemolytic streptococci, some of the outstanding features will be reviewed here.

Pneumonia due to hemolytic streptococci may either be a primary infection or be secondary to some other infection of the respiratory tract, such as acute coryza, epidemic influenza, measles, pneumococcic pneumonia or chronic disease of the respiratory tract. It commonly produces diffuse interstitial bronchopneumonia and is complicated by empyema in at least 25 per cent of cases. The fatality rate without chemotherapy varies between 25 and 40 per cent. With chemotherapy the fatality rate both for pneumonia and for empyema can be reduced; the course of the disease, however, may be indeterminate.

Inasmuch as this type of pneumonia is so often secondary to other infections, every effort should be made to protect patients with the infections just mentioned from coming in contact with those persons who carry hemolytic streptococci or who have clinical streptococcic disease.

Bacteremia.—In all, 37 different strains of hemolytic streptococci were isolated from the circulating blood, and we were able to type 32 of them. The results are recorded in table 2. As might be anticipated, the

16. Keefer, C. S.; Rantz, L. A., and Rammelkamp, C. H.: Hemolytic Streptococcal Pneumonia and Empyema: A Study of Fifty-Five Cases with Special Reference to Treatment, Ann. Int. Med. **14**:1533, 1941.

general distribution of the specific types in this study was the same as in the group as a whole. The common types, in order of frequency, were 15, 11, 13, 25 and 27.

The fatality rate for the group as a whole was 57 per cent. In another paper, one of us (C. S. K.) with associates [17] pointed out that without chemotherapy the fatality rate in bacteremia caused by hemolytic streptococci was 72 per cent and the factors influencing fatality were age, portal of entry, the presence of debilitating disease and the accessibility of the focus of infection for surgical drainage. Since all of the patients with bacteremia were treated with sulfanilamide, it was of interest to analyze the other factors which are known to influence prognosis under these circumstances.

TABLE 5.—*Correlation Between Fatality Rate and Age in Patients with Bacteremia*

Age, Yr.	Outcome		Total
	Recovery	Death	
10-20	7	0	7
21-30	2	2	4
31-40	5	3	8
41-50	1	5	6
51-60	1	3	4
61-70	..	7	7
70 or over	..	1	1
Total	16	21	37

Fatality rate for patients under 40 years, 26 per cent
Fatality rate for patients over 40 years, 88 per cent

Of the 16 patients who recovered, 14 were under 40 years of age and none was over 60 years of age. Of the 21 patients who died, 16 were over 40 years of age; the ages of the remaining 5 varied from 21 to 40 years. In the patients under 40 who died such conditions as acute endocarditis, alcoholism, puerperal sepsis or cirrhosis of the liver were present.

The fatality rate for patients under 40 years was only 26 per cent, whereas for those over 40 years it was 88 per cent, a striking difference. This is particularly impressive when it is compared with fatality rates for patients treated without sulfanilamide, since here the fatality rate for those under 40 years is about 60 per cent (table 5).

There did not seem to be any correlation between the type of organism and the frequency with which the blood was invaded when one took

17. Keefer, C. S.; Ingelfinger, F. J., and Spink, W. W.: The Significance of Hemolytic Streptococcal Bacteremia: A Study of Two Hundred and Forty-Six Patients, Arch. Int. Med. **60**:1084 (Dec.) 1937.

into account such factors as age, focus of infection and the presence of debilitating disease (table 6). For example take type 11. Of 6 patients with bacteremia caused by organisms of type 11, all died. With the exception of 1 patient who had puerperal sepsis, all of the patients were over 40 years of age and in all of them the portal of entry was the skin. We have shown previously that bacteremia following infections of the skin and the subcutaneous tissues is always associated with a high death rate in patients over 40 years of age. The importance of age is also brought out in the study of other types (type 15). Of the 5 patients who recovered, 4 were under 20 years of age and the other was 29 years old. Of the 10 patients who died, all but 1 were over 40 years of age, and the site of the infection was such that it could not be localized and drained surgically.

TABLE 6.—*Correlation Between Fatality Rate, Type of Invading Hemolytic Streptococcus and Age in Patients with Bacteremia*

	Age			
	Under 40 years		Over 40 Years	
Type	Recovered	Died	Recovered	Died
15	5	1*	0	9
11	0	1†	0	5
12	0	2	0	3
27	0	0	0	1
25	0	2‡	..	..
1	2	1§	0	0
13	1	0	0	1
Unidentified types	4	0	1	0

* Died of heart disease.
† Died of puerperal sepsis.
‡ Died of bacterial endocarditis and of chronic alcoholism.
§ Died of chronic alcoholism.

No evidence was obtained, therefore, which indicated that any particular type was more likely to invade the blood. Invasion of the blood was correlated more often with age, the focus of infection and the general condition of the patient than with the type of invading organism.

Abscesses.—Hemolytic streptococci were obtained from 58 abscesses, and 74 per cent of the strains were typed. They included, in order of frequency, types 11, 1, 13, 15, 27 and 28. These abscesses occurred in all parts of the body, including the throat, neck, extremities, pelvis, other bones, scrotum and the perirenal region.

Rhinitis.—Forty-one patients had rhinitis after scarlet fever. The common types causing this complication were type 13, isolated sixteen times; type 15, isolated six times, and an unidentified type, isolated 9 times. Other types were 2, 11, 25 and 10. Rhinitis was encountered in 16 per cent of all patients with infection caused by hemolytic streptococci of type 13.

Puerperal Sepsis.—Only 1 patient in this series had puerperal sepsis, but the important studies of Colebrook [11a] and of Butler and Hill [6a] are well worth reviewing in connection with this study, since they add valuable information concerning the mode of infection and the spread of puerperal sepsis. Colebrook's monograph is filled with information of the greatest value and importance, and every physician and obstetrician should be familiar with the facts that she brings out, in order that the occurrence of puerperal sepsis may be reduced or prevented. Some of the outstanding facts are the following ones:

1. Organisms which cause puerperal sepsis are not found in the vagina at the beginning of labor.

2. The most important sources of infecting organisms are in the human respiratory passages and in septic foci of infection.

3. The extragenital source of infection may be in the respiratory passages (nose or throat) of (*a*) the patient herself, (*b*) the members of her family or (*c*) her professional attendants. These persons may be healthy carriers, or they may have head colds with hemolytic streptococci in the nose and/or throat.

4. Organisms may be conveyed from the nose and throat of the patient or of "familial" contacts by means of her own hands or perhaps by towels which are contaminated by the secretions of the nose or throat.

5. Every parturient woman runs the risk of infection when her confinement is conducted in an infected environment. Attendant contacts are most frequent; household contacts are next in frequency, and autoinfection from extragenital sources are third.

6. Puerperal sepsis is most common during the season of the year when other infections caused by hemolytic streptococci are prevalent, and the types are those most frequently encountered in these infections.

Colebrook found types 1, 2, 5, 14 and 25 to be the commonest types isolated, but among 85 strains tested, 18 different types were identified. In Australia Butler and Hill [6a] were able to type 38 of 68 strains which were isolated from patients with puerperal sepsis. Types 22 and 27 and 1 type called "Woodbury" were responsible for the infections.

Diddle, Trussell and Plass [9d] described an epidemic of scarlet fever and other infections caused by hemolytic streptococci in an obstetric ward. An examination of this paper confirms the fact that puerperal sepsis is due to the spread of infection from the nose and throat to the uterus, as well as to or from other areas of the body. The predominating organism in this epidemic was type 3, and the orginal case was that of a parturient woman with a severe infection of the upper respiratory tract, which had been acquired during an unreported contact with a relative in the prodromal stage of scarlet fever. It was of interest that of the

persons who were exposed in the ward, an infection of the upper respiratory tract developed in 14 infants and severe tracheobronchitis due to hemolytic streptococci developed in 7 of the 14. Of the 66 adults who harbored hemolytic streptococci, 14 had typical scarlet fever, 2 had puerperal endometritis, 13 had pharyngitis, 5 had rhinitis and 32 were asymptomatic carriers. This epidemic illustrates how the organisms may spread from 1 person to a group and produce a wide variety of clinical infections.

De Waal [51] reported that the commonest types causing puerperal sepsis in Scotland are types 1, 4 and 28. Only 22 of 50 strains could be typed, but the type of hemolytic streptococci which predominated usually varied with the season of the year and reflected the epidemic type which was present in patients with scarlet fever at the time.

RELATION OF SPECIFIC TYPES TO SEVERITY OF INFECTION AND COMPLICATIONS

Attempts have been made by several investigators to correlate the severity of infection and the incidence of complications with certain specific types of streptococci. Gunn and Griffith [5d] in 1928 stated that type 1 seemed to produce the most severe disease and the most complications and type 2 was likely to cause nephritis and endocarditis. The number of cases studied was small. De Waal,[51] on the other hand, found that type 4 produced the most severe infections in Scotland and type 1 was responsible for mild attacks of scarlet fever. He stated that the complication rate in infections caused by organisms of type 1 was higher than that in infections caused by type 4 organisms and the complications in infections caused by type 1 organisms were frequently due to cross infection with those of type 4. He expressed the opinion that these organisms may become increasingly virulent or avirulent, depending on factors which are at present unknown.

It is a difficult matter to assess the relative severity of different infections unless one considers bacteremia and death as indicative of the most serious infections, as well as the total duration of the infection and the complications in those patients who survive. Even when one takes bacteremia as a criterion for severity of infection, it becomes apparent that there are many factors other than the type of infecting organism which influence the outcome. While blood cultures were not made for all patients who were studied in this group, bacteremia was present in 4.5 per cent of those for whom cultures were made.

The frequency with which various types were isolated from the blood varied from 1.4 per cent in type 13 to 8.0 per cent in types 25 and 27. That is to say, 1.4 per cent of all the type 13 strains we studied

were isolated from the circulating blood. On more careful analysis it was found that factors other than specific type determined the frequency of bacteremia. These were the age of the patient, the portal of entry and the general condition of the patient.

Other methods of correlating the severity of infection with the characteristics of the organisms have been used by Butler and Hill [6a] and White, Rudd and Ward.[6b] These investigators have found that encapsulated strains of hemolytic streptococci have greater infectivity than noncapsulated ones, and Butler and Hill expressed the opinion that encapsulated strains caused more severe infections and showed that 21 of 22 strains isolated from the blood stream were capsulated. White, Rudd and Ward were in agreement that capsulated strains are more likely to cause infection, perhaps due to their ability to resist phagocytosis, but asserted that once the tissues are invaded the noncapsulated organisms are just as virulent as capsulated strains.

In the present state of knowledge, it would be premature to say that some types of hemolytic streptococci are invariably more invasive and virulent than others. It does seem clear, however, that certain strains of hemolytic streptococci, regardless of their type, are more invasive and more virulent than others and that this is due in part to the organism's ability to resist phagocytosis. Before this question can be settled, it will be necessary to study and analyze many cases in which both the characteristics of the organism and the factors in the host are taken into consideration.

The determination of the relation between specific types and complications is a difficult problem, since many of the late suppurative complications are caused by a new type of organism or by cross infection. This aspect of the subject has been investigated by Gunn and Griffith,[5d] Brown and Allison,[5j] de Waal,[5l] Bailey [9e] and others. Brown and Allison [5j] made a most thorough study of the question both of complications and of relapses in scarlet fever and pointed out that no reinfections occurred in single-bed rooms or in wards in which the patients were all infected with the same type of organisms. In one ward of 47 patients, complications occurred in 20. In 18 the complication was due to a different type of organism from that which caused the original infection. In another group of 15 patients the infection was latent; that is, a different type of streptococcus was found without signs of complications. In 10 patients who showed relapses a new type of organism was found in the throat. It has been demonstrated by Gunn and Griffith [5d] that relapses of scarlet fever may occur in patients with a different type of organism who failed to give a negative reaction to the Dick test after the initial attack. Of considerable importance in the com-

plications due to a different type of streptococcus was the time of their occurrence. Sixteen of the 18 complications occurred during the second, the third and the fourth week of illness.

De Waal [51] has reported new types in 61 per cent of complications of scarlet fever in Edinburgh and in this way indicates that complications are frequently caused by reinfections. His results confirm those of Brown and Allison.[53]

Bailey [9c] stated that he was unwilling to accept the fact that complications are due to cross infection or reinfection, and based his opinion on his own studies, which were made in 1934 and 1935. He found that as many as 57.6 per cent of patients who were admitted to a hospital and in whom complications did not develop left the hospital with a type of streptococcus different from that which they harbored on admission. In another group of 18 patients with complications, 9 had a different type of streptococcus in the throat. He reported a general complication rate of 36 per cent ± 2.3 in 197 patients. Among 72 patients showing a type of hemolytic streptococcus on discharge which was different from that causing the disease, the complication rate was 25 per cent ± 3.4. He apparently felt so confident of the isolation technic in his hospital that he explained the differences in the types which were isolated early and late in the course of the disease on a basis of transmutation rather than cross infection. Certainly from the data presented by Bailey one may conclude that a patient may have a different type of streptococcus in the throat late in the course of the disease, with or without complications. This is in concurrence with the observations of others. There is no agreement, however, that organisms change from one type to another during the course of the disease. There seems to be little doubt, then, that complications may be due to the same type as that causing the original infection or that they may be due to a different type. Also, after an uncomplicated infection a patient may continue to carry the same type of organism in the throat when he is discharged from the hospital or he may carry one of a different type.

Our own observations concerning the relation of reinfection and complications were of interest. In 34 patients the type of the causative organism was known at the beginning of the infection and also at the time of the complication. The results are shown in table 7. In 12 patients the same type of hemolytic streptococcus was isolated from the throat during the original infection and during the complication in the first two weeks of the illness, and in only 3 was a different type found in the throat and middle ear. After the second week, however, there were only 2 complications due to the same type, whereas 16 were due to a different type. These observations certainly suggest that many of the late complications of scarlet fever are due to a different type of

organism from that isolated originally. When the complication occurs during the first two weeks, it is generally due to the same type of organism causing the initial infection. In all, 55 per cent of the complications were caused by a different type of streptococcus.

Recurrent Scarlet Fever.—Two patients had recurrent scarlet fever. Neither patient had received either sulfanilamide or convalescent serum, and in both cases the type of hemolytic streptococcus isolated during the recurrence was different from that which was isolated during the primary attack. In 1, types 8 and 15 were responsible for the 2 attacks, and in the other types 12 and 13.

There were 20 patients in whom no complications were present and in whom we typed the organism at the time of the initial infection and at the time of discharge. The same type was present on discharge in

TABLE 7.—*Relation Between Types of Hemolytic Streptococci Found During Original Infection (Scarlet Fever) and During Complication*

Interval Between Original Infection and Complication, Days		Same Type Isolated	Different Type Isolated
Same day		7	0
1-7		4	1
8-15		1	2
16-21		1	5
22-28		1	7
28		..	4
Under 2 weeks	Same type	12	
	Different type	3	
Over 2 weeks	Same type	2	
	Different type	16	

12 patients, but a different type was found in 8. This suggests that a patient with scarlet fever may become a carrier of an organism of a different type from that causing the original infection. While we were unable to trace the source of the cross infections in these patients, the types which were isolated during the complication were prevalent in the hospital at the same time, so that the most likely explanation, taking everything into consideration, is that the cross infection took place either directly from other patients by means of transmission through the air or by contact with attendants. That this is the usual explanation there can no longer be any doubt.

Indirect evidence for cross infection is found in a study of the types in multiple cases in the same family. There were ten families in which more than 1 member had scarlet fever at the same time. In each family group the same type of hemolytic streptococcus was responsible for the scarlet fever. This fact has been stressed by Bradley [9a] and de Waal.[51]

From our own studies and those reported in the literature, the relation of specific types to the severity of infections caused by hemolytic streptococci and complications may be summed up as follows:

1. There is insufficient evidence at present to state whether any specific type is likely to cause more serious disease or more frequent complications. It would appear that other factors aside from the specific type of organism are equally important, such as the presence or absence of capsules, age of the patient, portal of entry and whether the blood is invaded by the organism.

2. The chief value of typing at present seems to be in studying the epidemiologic aspects of infection. This includes its mode of spread and the cause and mechanism of complications. All of these facts aid in prophylaxis.

3. When multiple infections caused by hemolytic streptococci occur in families, they are usually due to organisms of the same type.

4. When complications occur early in the course of the infection, i.e., during the first two weeks, the same type of streptococcus is usually found in the area of complicating infections. When the infection occurs after the second week, a different type of organism is frequently found. These observations suggest that many late complications are due to cross infections and, therefore, are true reinfections.

5. A patient can become a carrier of a different type of streptococcus from that causing his illness without displaying any signs of complications.

STREPTOCOCCIC DISEASE CAUSED BY ORGANISMS OF DIFFERENT TYPES

Type 1.—Streptococci of this type were isolated chiefly from patients with scarlet fever, tonsillitis, otitis media and mastoiditis. They were found also in persons with erysipelas and pneumonia and in circulating blood. They caused otitis media in 20 per cent of the patients with scarlet fever. They were more often the cause of otitis media without preceding scarlet fever than with preceding scarlet fever. On three occasions type 1 organisms were isolated from the circulating blood. There was no evidence in the small number of patients studied that infection caused by this type was more severe than infections caused by other types.

Type 2.—Organisms of this type were isolated mainly from persons with scarlet fever, otitis media, mastoiditis and pneumonia. The infections were relatively mild without complications.

Type 11.—Organisms of this type were third in order of frequency in the entire series. They caused scarlet fever, tonsillitis, otitis media, abscesses and erysipelas and invaded the blood of 6 patients. The

incidence of otitis media was greater without preceding scarlet fever than it was with it. This was the commonest specific type isolated from persons with mastoiditis and from localized abscesses. The invasion of the blood occurred in elderly persons with cellulitis or cutaneous lesions.

Type 13.—This type was second in order of frequency, causing mainly scarlet fever, tonsillitis, otitis media and mastoiditis. Twelve per cent of the infections due to this type were scarlet fever complicated by otitis media. Organisms of type 13 were also isolated from persons with pneumonia and empyema and from abscesses and the circulating blood.

Type 15.—This was the commonest type, and the organisms were isolated from persons with scarlet fever, otitis media and mastoiditis and pneumonia and empyema and from circulating blood and abscesses. It was the cause of erysipelas and meningitis in 1 patient each. This is one of the common types causing scarlet fever in Scotland and in Australia.

Type 25.—Organisms of this type were isolated from persons with otitis media and mastoiditis, tonsillitis and scarlet fever and from abscesses and the circulating blood.

Type 27.—Streptococci of this type had the same distribution as those of type 25.

Other Identified Types.—Types 5, 6, 8, 9, 10, 14, 19, 21, 26, 28 and 29 were responsible for a few of the infections listed in the table.

Unidentified Types.—Types which could not be identified accounted for 180 infections.

COMMENT

We may now ask the question, what have these observations contributed to the information concerning infections caused by hemolytic streptococci and of what value is the typing of hemolytic streptococci in the study of various diseases? It will be generally agreed that the treatment of such infections has been revolutionized during the past six years because of the introduction of sulfanilamide and its derivatives. It is plain, however, that the fatality rate continues to be high in certain of these infections, especially when they occur in aged persons, and the time lost from these different diseases continues to be considerable. The problem of prevention of infection caused by hemolytic streptococci, therefore, becomes one of the major considerations in this field. In order to prevent a disease, its cause and mode of spread must be known. By means of specific typing, information concerning the mode of spread and the sources of infection can be obtained. At present, this would appear to be its greatest field of application. It may also be of value in explaining the difference in severity of various infections, although

from the evidence that has accumulated thus far it appears that there are other factors aside from specific types which are equally or more important.

Typing of hemolytic streptococci has also settled the long controversy concerning the specificity of hemolytic streptococci with reference to particular diseases. It is now clear that factors other than the organism are operative in the production of various clinical entities. The same specific type of hemolytic streptococcus may cause scarlet fever, tonsillitis, otitis media, mastoiditis, erysipelas or puerperal fever. The view that specific streptococci are responsible for specific diseases is no longer tenable.

Typing of organisms has also assisted in explaining relapses in patients with scarlet fever and late complications, since relapses are due to a reinfection by a different type of organism in a person in whom toxic immunity has failed to develop, and many of the late complications are due to reinfections.

Finally, it has provided suggestions which should be of great assistance in controlling the spread of infections.

We may now discuss some of the facts which are concerned with the mode of spread of diseases caused by hemolytic streptococci and which have been placed on a firm foundation by means of specific typing and accurate identification of organisms. The normal habitat of the hemolytic streptococcus is in the throat and nose, so that there are many carriers in the general population. The carrier rate increases during the winter months when streptococcic diseases are prevalent and when healthy persons come in contact with patients with these diseases. Such infections are more common when head colds are frequent. A person may be predisposed to infection by hemolytic streptococci; if he carries the organisms prior to the development of a cold, he can disseminate them more readily when the cold is active. The carrier state may be permanent or transitory, and the specific types carried may vary from time to time, depending to some extent on the carrier's contacts.

Since the normal habitat of hemolytic streptococci is in the throat and nose, and since the commonest sites for acute infections due to these organisms are in the same region of the body, it is not surprising that infections caused by hemolytic streptococci, regardless of their location, have their original source in the nose or throat. Therefore, carriers, and especially persons with head colds, who harbor hemolytic streptococci or persons with tonsillitis, pharyngitis, sinusitis or scarlet fever may all serve as sources of infection. From the nose and throat, infection may spread from one person to another by means of contact, i.e., transmission of air-borne organisms (coughing, sneezing, dust particles), contamination of the hands or fomites (towels, toys, food) with infected material.

By means of specific typing, then, it has been possible to show that hemolytic streptococci are spread in these ways. A few examples will serve to support these statements:

1. Multiple infections caused by hemolytic streptococci in families and schools or other institutions are usually due to the same type of organism, regardless of the clinical forms of the disease.

2. Epidemics of infection caused by hemolytic streptococci can often be traced to a single patient with the disease.[18] A single patient with sore throat or scarlet fever may be responsible for other instances of similar disease or for puerperal sepsis, tracheobronchitis, pneumonia or erysipelas in contacts.

3. Puerperal sepsis may arise from persons who carry hemolytic streptococci in their throats or have septic foci. They may also arise from the patient herself; that is, the uterus may be infected through the medium of the patient's hands if she carries organisms in her throat.[11a]

Examples of this kind might be multiplied many times, but these serve to illustrate how infections may spread.

What can one do, then, to prevent the spread of hemolytic streptococci and reduce the number of cases of disease?

The clinical picture of scarlet fever can be prevented by prophylactic inoculation with toxin or toxoid. Whether such prophylactive inoculation reduces the incidence of infections in the throat without a rash or the other clinical manifestations of intoxication is difficult to decide with the evidence at hand, since in most of the reports which have dealt with the subject of prophylactic inoculation, the authors stressed the decrease in the frequency of the clinical picture of scarlet fever and made no statement about the incidence of streptococcic pharyngitis or tonsillitis in an inoculated group. According to some reports, the incidence of tonsillitis has remained the same in an inoculated group as in a non-inoculated group. According to others, it has been reduced. From the study of epidemics of scarlet fever in institutions, there seems to be good evidence that the clinical picture of scarlet fever does not develop in the children who give negative reactions to the Dick test, but that tonsillitis is prevalent and is caused by the same type of organism as that causing scarlet fever in others. In any event, it would seem to be a wise practice to immunize all professional attendants who give positive reactions to the Dick test and who come in contact with persons with scarlet fever and thus to prevent the symptoms and signs due to the toxin should an infection of the throat develop in such attendants.

18. Footnote 9 *d*, *e* and *g*.

Attempts have been made to protect groups who are susceptible to tonsillitis by vaccination [19] or by the use of sulfanilamide.[20] So far the evidence that either one of these measures is effective is too meager to warrant any conclusions. One must remember that the most susceptible persons are children between the ages of 5 and 15 years and those who are commonly exposed (nurses, attendants, physicians, school children and children in institutions).

The prevention of the spread of infections by contact can be minimized by means of isolation. The isolation of patients with scarlet fever and tonsillitis is easier than the isolation of patients with streptococcic pharyngitis and persons with head colds who carry organisms, because the patients in the former group have constitutional symptoms and a clinical disease which is readily recognized as being due to hemolytic streptococci. Even with good isolation technic in wards in a hospital, cross infection is not infrequent. Whether the methods of air conditioning or air sterilization in institutions and schools will reduce these cross infections still further only additional study will decide. In any event, before these infections can be reduced it will be necessary to develop practical methods for the prevention of the spread of organisms from one person to another.

SUMMARY AND CONCLUSIONS

During the years 1938 and 1939, 819 strains of group A hemolytic streptococci were studied in relation to their type specificity, the disease, the severity of infection and the occurrence of complications. The organisms were isolated from persons with scarlet fever, tonsillitis, erysipelas, abscesses, pneumonia, meningitis, and otitis media, with or without associated mastoiditis, and from nasal swabs and circulating blood. Of the 819 strains, we were able to type and identify 79 per cent with the serums that were available. As a result of these studies the following facts emerged:

1. The commonest types causing disease were 15, 13, 11, 1, 2, 25 and 27.

2. A number of types which cause disease are not included in the original Griffith strains.

3. The distribution of specific types varied from that which has been reported elsewhere. This is what might be expected in view of the

19. Bloomfield, A. L., and Felty, A. R.: Prophylactic Vaccination Against Acute Tonsillitis, Bull. Johns Hopkins Hosp. **12**:1473, 1939.

20. Thomas, C. B.; France, R., and Reichsman, F.: Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, J. A. M. A. **116**:551 (Feb. 15) 1941.

previous studies from other countries, since it has been shown that the predominating types vary from one community to another, from year to year and from epidemic to epidemic.

4. The same type may be responsible for different clinical diseases, that is, scarlet fever in 1 person, tonsillitis in another, erysipelas in a third and rhinitis in a fourth. This is striking in family epidemics of infection caused by hemolytic streptococci.

5. When one or more types are predominant in any community, the same types are usually isolated from persons with various diseases, such as scarlet fever, tonsillitis and otitis media.

The various types which were isolated during this study were discussed from the angle of the disease they caused, the severity of the infection and the ensuing complications. The following facts are significant:

1. When multiple instances of infection occur in families, institutions and schools, they are usually due to the same type of organism.

2. Epidemics of puerperal sepsis, tonsillitis, scarlet fever or other streptococcic infections can be traced to their source by means of typing the organism in different persons, usually contacts.

3. There is insufficient evidence available at present to determine whether some types cause more serious infections or a greater number of complications than others. There is substantial evidence, however, to suggest that factors other than the specific type of causative organism are important in determining the severity of infection and the incidence of complications. They include the age of the patient, the portal of entry, the presence or absence of debilitating disease, the general condition of the patient and the occurrence of reinfection.

4. When complications occur during the course of scarlet fever, they may be due to the same type of organism which caused the initial infection or to a different type. Complications occurring during the first two weeks of illness are frequently due to the same type; those developing later are often due to a different type. These observations suggest that late complications are due to reinfection.

The significance of these observations is discussed.

Miss Marjorie Jewell and Miss Eleanor Fleming gave technical assistance. Dr. W. G. Malcom, of the Lederle Laboratories, Inc., supplied us with the specific typing serums which were used in this study.

EFFECT OF MORPHINE AND DILAUDID ON THE ILEUM AND OF MORPHINE, DILAUDID AND ATROPINE ON THE COLON OF MAN

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CHICAGO

Plant and Miller [1] originally demonstrated that morphine in ordinary doses does not place the human intestine and colon at rest. This observation has been adequately confirmed. However, some authors have reported that the stimulation of motility, depending on the dose, is brief (twenty to sixty minutes) and is followed by depression,[2] and others have observed that the stimulation is of much longer duration.[3] It has been amply demonstrated that morphine delays the passage of material through the alimentary tract,[4] but the cause of the delay has not been clearly established.

Functionally, gastrointestinal motility is of two general types, namely, propulsive and nonpropulsive.[5] In the dog morphine affects these two

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Dr. Peter Rosi aided us in securing subjects.

1. Plant, O. H., and Miller, G. H.: Effects of Morphine and Some Other Opium Alkaloids on the Muscular Activity of the Alimentary Canal, J. Pharmacol. & Exper. Therap. **27**:361, 1926.

2. (*a*) Abbott, W. O., and Pendergrass, E. P.: Intubation Studies on the Human Small Intestine, Am. J. Roentgenol. **35**:289, 1936. (*b*) Hertzler, A. E.: The Effect of Morphine on Intestinal Motility, J. Kansas M. Soc. **40**:197, 1939.

3. (*a*) Orr, T. G., and Carlson, H. E.: Effect of Morphine on the Movements of the Small Intestine and Sphincter Muscles, Arch. Surg. **27**:296 (Aug.) 1933. (*b*) Yonkman, F. F.; Hiebert, J. M., and Singh, H.: Morphine and Intestinal Activity, New England J. Med. **214**:507, 1936.

4. (*a*) Meyers, G. N., and Davidson, S. W.: An Investigation of the Effects of Certain Substitutes for Morphine and Heroin upon the Passage of Food Along the Alimentary Tract of the Human Subject, J. Hyg. **38**:432, 1938. (*b*) Pancoast, H. K., and Hopkins, A. H.: Effect of Moderate Doses of Some Opium Derivatives on the Gastro-Intestinal Tract of Man, J. A. M. A. **65**:2220 (Dec. 25) 1915.

(Footnotes continued on next page)

types of motility differently.[6] The propulsive activity is temporarily increased and is then abolished, while nonpropulsive activity is increased for several hours. Whether morphine similarly affects the motility of the human small intestine and colon has not been adequately determined, nor has the action of dilaudid been similarly studied. We have investigated these problems and, in addition, have ascertained the effect of atropine on the changes in motility induced in the colon of man by morphine. A similar study has been made adequately by us on the dog with the idea in mind that the morphine-induced, hypertonic, nonpropulsive type of motility might be used to assay the effectiveness of antispasmodics on the colon of man.[6b]

PROCEDURE AND METHOD

Small Intestine.—We employed as a subject a patient who had undergone an ileostomy two years previously for ulcerative colitis. The patient was in excellent physical condition, was 38 years of age and weighed 140 pounds (63.5 Kg.). He was kept under our observation and dietary control for an experimental period of three months. During these three months experiments of three hours' duration were conducted twice daily.

A balloon or balloons in tandem were inserted through the orifice of an ileostomy bag. This permitted observation of the nonpropulsive motility, quantitative collection of the ileal discharge and quantitative evaluation of propulsive motility.

Colon.—Four men on whom colostomy had been performed six to eighteen months previously were the subjects. The rectum and one half of the sigmoid colon had been removed for carcinoma. The patients were in excellent physical condition, and no evidence of metastases was manifest. For six months 1 or 2 experiments, each three hours in duration, were conducted daily.

One or two balloons in tandem were inserted through the fistula into the descending colon; thus, the motility of the colon caudad the splenic flexure and 3 or 4 inches (7.5 to 10 cm.) cephalad the fistula was studied. More balloons in tandem or the motility of the transverse colon was not studied because on several occasions the balloon cephalad was tied by the colon into a simple knot, which rendered it difficult to remove in the presence of the hypertonicity of the colon induced by drugs. The balloons were all inflated according to a standard technic.[6b] Propulsive motility was evidenced and recorded by the outward movement of the tube from the fistula and the passage of gas and feces.[7]

Controls.—The patients were highly cooperative and permitted the repetition of tests many times. For example, 22 three hour balloon studies serving as a

5. (*a*) Quigley, J. P.; Highstone, W. H., and Ivy, A. C.: A Study of the Propulsive Activity of a Thiery-Vella Loop of Intestine, Am. J. Physiol. **108:** 151, 1934. (*b*) Reid, P. E.; Ivy, A. C., and Quigley, J. P.: Spiral Propulsion of a Bolus in the Intestine, ibid. **109:**483, 1934.

6. (*a*) Templeton, R. D., and Adler, H. F.: The Influence of Morphine on Transportation in the Colon of the Dog, Am. J. Physiol. **131:**428, 1940. (*b*) Adler, H. F., and Ivy, A. C.: Morphine-Atropine Antagonism on Colon Motility in the Dog, J. Pharmacol. & Exper. Therap. **70:**454, 1940.

7. Adler, H. F.; Atkinson, A. J., and Ivy, A. C.: A Study of the Motility of the Human Colon: An Explanation of Dysynergia of the Colon, or of the "Unstable Colon," Am. J. Digest. Dis. **8:**197, 1941.

control series were made on the patient who had undergone ileostomy. Sixty-seven similar control studies were made on those on whom colostomy had been performed. Hence, we were able to obtain as complete a picture of the motility of the human colon, with individual spontaneous variations, as of the canine colon.

Types of Motility Observed in the Human and the Canine Colon.—The three types of motility (fig. 1) manifested by balloon records of the human and the canine colon are similar.[8] Type I contractions are rather rapid and may occur in the presence of high or low tone and in any segment of the colon. Type I contractions on high tone are frequently seen after the administration of morphine. This type is rarely associated with the propulsion of contents, unless it occurs rather suddenly and in an exaggerated form, as after the administration of morphine. Even then, after the initial change of tonus level, propulsion does not occur if the tonus level is maintained. The type II contractions are characterized by their larger amplitude, longer duration and the superimposition of type I contractions. This type of contraction is frequently propulsive in nature. Whether contents are propelled, however, depends on the amplitude of the contraction, on the consistency of the contents and on the relation the contracting

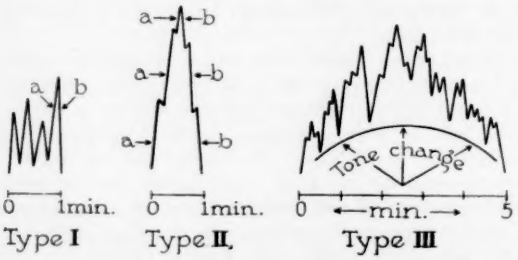

Fig. 1.—A diagrammatic representation of the manner in which complex contraction patterns are built up from more simple contractions. Type I contractions occur at the rate of 3 to 8 per minute and consist of a rapid contraction (*a*) followed by rapid relaxation (*b*). Type II contractions consist of contraction limbs made up of superimposed type I contractions. Type III contractions have a pattern consisting of type I and II contractions superimposed on a definite change in tonus.

segment bears to the motility of the adjacent segments. For example, if a segment manifests a type II contraction and the adjacent segment caudad exhibits type I activity on tone, the former contraction does not cause propulsion of contents unless motility of the segment caudad suddenly changes toward type II. Type III contractions are characterized by a definite tonus change of variable duration on which type II contractions of varying amplitude are superimposed. The change in tonus, or slow contraction, on which the type II contractions are superimposed usually does not last longer than twelve minutes in man. When this type of contraction occurs, it is usually followed by a period of quiescence.[8]

8. Templeton, R. D., and Lawson, H.: Studies on the Motor Activity of the Large Intestine, Am. J. Physiol. **96**:667, 1931. Adler, Atkinson and Ivy.[7]

The initial type II contractions which are manifested during the rise in tone are chiefly responsible for the propulsion that occurs during this type of contraction.[9]

It is important to point out that the type of motility of one segment may be quite different from that of adjacent segments. Significant propulsion, as occurs in "mass peristalsis," is not exhibited until the motility of adjacent segments becomes coordinated, so that type II waves pass successively in a synergized manner to and over the more caudal segments. The importance of this concept in relation to the explanation of the "irritable colon," which is viewed as "dyssynergia of the colon" has been indicated in a previous article.[7]

RESULTS

ILEUM

Effect on the Motility of the Human Ileum of the Intramuscular Injection of Five, Eight, Ten and Sixteen Milligram Doses of Morphine Sulfate.—The subject ate the same breakfast and lunch each day. Soon after he had finished breakfast the residue of the previous evening dinner was passed into the ileostomy bag. The breakfast taken at 8 a. m. would normally begin to appear definitely after 11 a. m., the subject being under observation from 9 a. m. to about 12 noon. At 12 noon lunch was ingested, and soon after the residue from breakfast was passed. The subject was then under observation until 4:30 p. m. At about 4 or 4:30 p. m. the luncheon residue would begin to appear in the ileostomy bag.

Balloon Records of Motility: After a control record was obtained for twenty to forty minutes, the morphine sulfate was injected. During the control period the ileum was relatively quiet because of the aforementioned previous evacuation. After a latent period of five to twenty minutes, depending usually on the size of the dose of morphine, the tone of the ileal segment started to increase. The tonus level rose to a plateau, at which variations in tone occurred on which rhythmic contractions of larger amplitude than those of the control period were manifested at a rate of 3 to 9 per minute (fig. 2 *A*). This type of response was observed in 12 of 18 experiments with the various doses of morphine. In 3 experiments no significant change occurred, and in 3 there was a decrease in tone.

Propulsive Motility: In the dog shortly after the injection of morphine an increase in tone and propulsive motility occurs which lasts twenty or thirty minutes, after which propulsive activity decreases or is absent and nonpropulsive activity and tone continue to be augmented for several hours. The early increase in propulsion is less evident in the ileum than in the jejunum.[5a]

9. Adler, H. F., and Templeton, R. D.: The Correlation of Activity and Transportation in the Colon of the Dog, Am. J. Physiol. **128**:514, 1940. Adler, Atkinson and Ivy.[7]

According to our observations on the human subject, no increase in propulsive activity occurred after the injection of morphine. The propulsive activity was diminished throughout the period of observation.

Amount of Contents Collected from the Ileostomy Bag: In correlation with what one would predict from the motility records of the lower portion of the ileum, it was found that less material was ejected into the ileostomy bag after the administration of morphine than when morphine

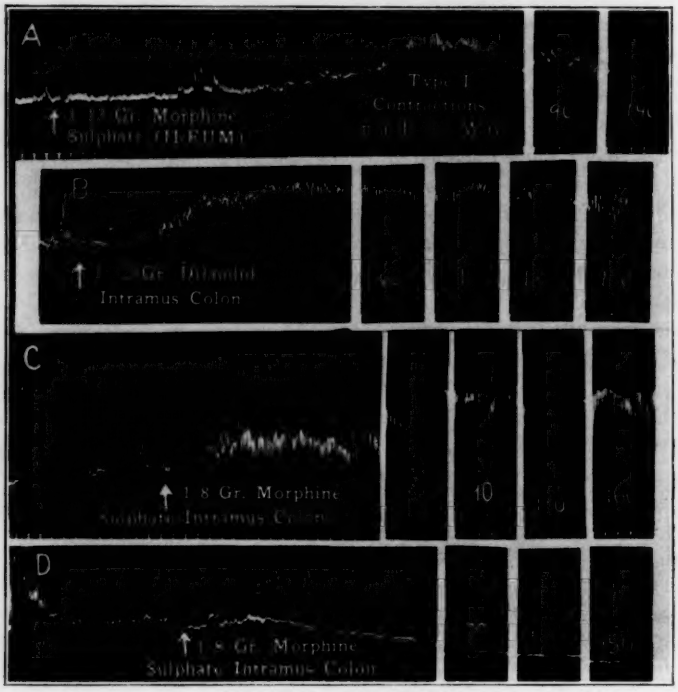

Fig. 2.—*A*, the reaction of the human ileum to 1/12 grain (0.005 Gm.) of morphine sulfate includes a rise in tonus and the appearance of type I contractions. *B*, the reaction of the human colon to 2 mg. of dilaudid hydrochloride. A rise in tonus and type I contractions (at a slower rate than in *A* or *C*) are evident. *C*, the reaction of the human colon to 8 mg. of morphine sulfate includes the appearance of type I contractions and a rise in tone. *D*, the reaction of the colon of the patient referred to in *C* to another 8 mg. dose of morphine sulfate. There is a definite decrease in tonus, but small type I waves are present.

was not given. During the 22 three hour control experiments an average of 90 cc. of contents was collected, the range being 72 to 115 cc. In the 18 three hours experiments with morphine an average of 35.6 cc. of con-

tents was collected, the range being 15 to 50 cc. Thus, morphine in the doses used consistently diminished the discharge of contents from the ileum.

Effect on the Motility of the Human Ileum of the Intramuscular Injection of One and Two Milligram Doses of Dilaudid Hydrochloride.—In 9 experiments the injection of 1 or 2 mg. of dilaudid hydrochloride caused the same type of response in the ileum as was obtained with morphine. One milligram of the drug appeared to have the same effect as 8 to 10 mg. of morphine sulfate. On 3 occasions when 2 mg. of dilaudid hydrochloride was administered the patient became nauseated, the nausea culminating in emesis once.

Dilaudid caused a decrease in the amount of contents discharged into the ileostomy bag. The amount collected ranged from 24 to 47.6 cc. for the three hour period, the average being 31 cc.

COLON

Effect on the Motility of the Human Colon of the Intramuscular Injection of Five, Eight, Ten and Sixteen Milligram Doses of Morphine Sulfate.—The patients evacuated the distal portion of the colon by enema each morning after breakfast. Normally no further material was passed until lavage the next morning. Thirty-three experiments of three hours' duration were performed in which morphine sulfate was administered in doses of 8, 10 and 16 mg. to these patients, who weighed from 160 to 190 pounds (72.6 to 86.2 Kg.). A twenty to forty minute control record was made before the drug was given. The records of these experiments were compared with those of 67 control periods of three hours' duration. The total motility and the propulsive motility were measured by a method described previously.[10] Effective propulsive activity was evidenced by the outward passage of the tube or tubes or by the passage of gas and fecal material.

In 25 of the 33 experiments an increase in tone occurred five to nine minutes after the injection. Type I contractions (fig. 2*C*) at a rate of three to eight per minute were superimposed on the high tone. In 9 experiments a definite decrease in tone occurred in one of the particular segments under observation (fig. 2*D*). (The waves seen in figure 2*D* are not due to respiration, but are type I waves superimposed on low tone.) No relation was noted between the tone and the motility existing at the time of injection of morphine and the type of motor response elicited by the drug.

10. Borkon, E. L., and Templeton, R. D.: The Influence of Oil Enemas on Colon Motility in the Dog, Am. J. Physiol. **118**:775, 1937.

In 7 experiments 5 mg. of morphine sulfate was administered. As in the study of the ileum, this dose was not sufficient to cause the typical response observed after larger doses. A fairly typical response occurred in only 4 experiments; in 3 others the change in motility was not definite.

The data on the total motility and the propulsive motility are shown in the table. It is to be noted that after the administration of 8, 10 and 16 mg. of morphine sulfate the average total motility is decidedly increased, whereas the propulsive motility is decreased.

The most constant effect of the drug, other than an increase in the tone of the segment of the colon being studied, was a marked decrease in the propulsive motility. After the administration of morphine no fecal material was expelled. This was dramatically manifested on 9 occasions during the course of our studies when the patients reported for

Quantitative Data Pertaining to the Action of Morphine, Dilaudid and Atropine on the Human Colon

No. of Tests on Four Subjects	Substance Administered	Total Motility,* 50 Min. Periods			Propulsive Motility,† 50 Min. Periods		
		1	2	3	1	2	3
67	Control	53	57	50	13	10.5	7.5
33	8, 10 and 16 mg. of morphine sulfate	87	91	89.4	3.1	2.4	3.8
16	2 mg. of dilaudid hydrochloride	86	85	88.5	4.1	2.3	4.3
10	0.7 and 0.8 mg. of atropine sulfate	34	27.6	38.5	2.8	3.2	3.6
6	8 mg. of morphine sulfate and 0.7 mg. of atropine sulfate	64	69.3	68.4	2.0	1.8	2.3

* Total motility, the percentage of the 50 minute experimental period during which the colon is active.

† Propulsive motility, a percentage of the total motility.

study with hypermotility of the colon of unknown cause except in 1 instance of overindulgence in alcohol. On these occasions fluid material was being intermittently and copiously discharged from the fistula with type II contractions of high amplitude. The administration of morphine completely abolished the discharge, not by reducing the quantity of motility, but by increasing the nonpropulsive motility and decreasing markedly the propulsive type of motility.

Effect on the Motility of the Human Colon of the Intramuscular Injection of Two Milligrams of Dilaudid Hydrochloride.—Sixteen experiments were performed. In 13 the tone of the segment of the colon being studied was decidedly increased; in 3 it was decreased. Figure 2 *B* illustrates the usual effect of 2 mg. of dilaudid hydrochloride. As in the case of a dose of 8 to 16 mg. of morphine sulfate, 2 mg. of dilaudid hydrochloride increased the tone of the colon and the amplitude of the type I nonpropulsive contractions. Thus, 2 mg. of dilaudid hydro-

chloride had approximately the same effect on the colon as 8 to 16 mg. of morphine sulfate. The quantitative data are shown in the table.

Effect on the Motility of the Human Colon of the Subcutaneous Injection of Seven-Tenths and Eight-Tenths Milligram Doses of Atropine Sulfate.—We administered atropine in ordinary therapeutic doses to our subjects primarily as a control for the group of experiments on atropine-morphine antagonism. However, we were also interested in the use of such doses because Cushny [11] and Bastedo [12] have stated on questionable grounds that atropine is practically without effect on the movements of the colon.

The dose of atropine used caused some drying of the mouth in our 4 patients. This fact was elicited by questioning and was not a spontaneous complaint. The spontaneous motility of the colon was diminished in all 4 subjects. It was completely abolished in 5 tests. In 3 other tests the amplitude and duration of the movements were decreased, and the quiescent periods were lengthened. In the 2 other tests only mild nonpropulsive activity was present. The average results are shown in the table.

It should be pointed out that with the multiple balloon technic it has been observed that in the dog atropine affects some segments of the colon more definitely than other segments.[6b] The distal portion of a dog's colon is more sensitive to the motor inhibitory action of atropine than is the proximal portion. These observations have to be considered in the interpretation of results for the human colon obtained with the use of a single balloon.

Effect of Morphine-Atropine Antagonism on the Human Colon.—In a previous study on the dog two of us (H. F. A. and A. C. I.) found that 1 mg. of atropine sulfate (0.028 to 0.052 mg. per kilogram of body weight) will antagonize the effect of 4 mg. of morphine sulfate on the colon.[6b] In the present study we have determined whether atropine antagonizes any of the stimulating effects of morphine on the colon of man.

In 6 three hour experiments on the 4 patients 0.7 mg. of atropine sulfate was given with 8 mg. of morphine sulfate. Other experiments were not performed because the results were consistent and correlated well with the results obtained on the dogs. Larger doses of atropine were not used, as was done in the case of the dogs, because of the disagreeable effects.

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11. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, ed. 11, Philadelphia, Lea & Febiger, 1936.

12. Bastedo, W. A.: The Value of Atropine and Belladonna in Stomach Disorders, J. A. M. A. **106**:85 (Jan. 11) 1936.

The atropine antagonized definitely, though not completely, the stimulatory effect of morphine on the tone and the type I motility. The average results are shown in the table. As might be expected, the atropine tended to augment the inhibitory effect of morphine on propulsive motility.

COMMENT

Numerous studies on the effect of morphine on the human ileum and colon have been conducted. The characteristic feature of these studies is that more than 1 experiment on each subject has rarely been made and evidence of a quantitative nature is lacking. This we believe is the chief reason for the differences in opinion regarding the effect of morphine on the small intestine and colon of man. Another reason is the fact that any two segments of the colon do not necessarily react identically to a drug and that many authors do not distinguish between nonpropulsive and propulsive activity. This distinction cannot be made by balloon records alone. Some do not consider the fact that spontaneous changes in the type of motility occur. Unless one has control records for the same subject made over a relatively prolonged period under controlled dietary and other conditions in which no experimental variation is introduced, errors in interpretation are likely to result. In our studies, which were preceded by similar studies on the dog, the foregoing factors have been considered and quantitative data are provided.

Ileum.—In regard to the effect of morphine and dilaudid on the ileum of our subject, the administration of 8, 10 and 16 mg. doses of morphine sulfate or dilaudid hydrochloride in doses of 1 or 2 mg. definitely increased the tone and the nonpropulsive motility of the ileum.

These drugs definitely reduced the discharge of intestinal contents from the opening created by ileostomy over a three hour period of observation. The interpretation of what constitutes an effective peristaltic movement is the only real difference between our observations and those of Plant and Miller,[1] Abbott and Pendergrass,[2a] Yonkman, Hiebert and Singh [3b] and Puestow,[13] whose articles adequately reviewed the literature (see also Krueger [14] and Orr and Carlson [3a]). We believe that one cannot objectively determine whether a movement of the bowel is effectively peristaltic by a balloon record. To determine whether a movement represents effective peristalsis, we believe its push or pull, as demonstrated elsewhere,[15] or the propulsion of contents must occur and be measured.

13. Puestow, C. B.: Intestinal Motility of Dog and Man, in Illinois Medical and Dental Monographs, Urbana, University of Illinois Press, 1940, vol. 2, no. 2.

14. Krueger, H.: The Action of Morphine on the Digestive Tract, Physiol. Rev. **17**:618, 1937.

15. Adler and Ivy.[6b] Cushny.[11]

On the basis of our motility records supported by the actual measurement of contents expelled from the ileostomy with and without morphine, it is evident that morphine increased ileal passage time, or "constipated" the ileum, in our subject in the presence of an increase in tone and nonpropulsive movements. The fact that churning movements may occur and produce borborygmi is evidence of increased activity but not evidence of increased rate of propulsion along the bowel. This is confirmatory of the roentgenologic observations of Abbott and Pendergrass,[2a] who observed a long delay in the time of passage from the intestine to the cecum and of the clearance of barium sulfate from the intestine after morphine was given. The pooling of barium sulfate in certain segments separated by nonfilled segments, or a "sausage string" effect, is compatible with the presence of increased tone and amplitude of nonpropulsive movements and the fact that all segments are not similarly affected by a drug at the same time. If the contents are not propelled, it is natural for pooling to occur with churning, provided one segment is more tonic than another. Synergistic or coordinated activity between segments would seem to be necessary for effective propulsion of contents. This type of activity is apparently embarrassed by the effect of morphine on the small intestine. Our interpretation of our own observations and of those of other investigators is that morphine produces dyskinesia or an imbalance between the nonpropulsive and the propulsive movements of the small intestine by increasing the nonpropulsive activity. Whether the drug acts directly on the intestine to augment nonpropulsive activity and to depress propulsive activity or whether it only augments nonpropulsive movement, which in turn depresses propulsive activity, is uncertain.

Colon.—The injection of ordinary therapeutic doses (6 to 16 mg.) of morphine sulfate, as almost every one agrees who has made single injections, causes an increase in the tone and the rhythmic movements of the colon. However, Pancoast and Hopkins,[4b] using the fluoroscope, observed variable results. Puestow,[13] who studied by inspection the everted cecum of a patient, observed only relaxation and local rhythmic waves. That this is rather unusual is shown by the graphically recorded results of Yonkman and associates,[3b] who observed that the injection of morphine was followed by an increase in the tone and the activity of the cecum of 3 patients who had undergone cecostomy. No one has apparently observed a relaxation of the distal portion of the colon of man after the administration of morphine. However, in 9 of 33 tests we observed relaxation in one of the segments of the descending colon being studied. The 9 instances of relaxation did not occur in any 1 subject and were unrelated to the type of motility present at the time of injection.

The fact, which is clearly evident in the colon of the dog when it is studied by the multiple balloon technic, that all segments of the colon do not respond alike at the same time to a drug might explain the relaxation observed by Puestow and the variable response reported by Pancoast and Hopkins (see the preceding paragraph). The fact that relaxation or loss of tone may occur in one segment during a period of ten or twenty minutes in which an adjacent segment may show an increase in tone in response to morphine indicates that the pooling of barium sulfate, or the "sausage string effect," noted in the small intestine by Abbott and in the colon by Jackman and Bargen [16] may be due to an actual relaxation of the segment. This relaxation may be due to the direct effect of morphine on the segment or to a reflex effect from the adjacent hypertonic segment. This evidence of dyskinesia of the colon along with the definite decrease in propulsive activity, as revealed by our balloon records and by the lack of expulsion of contents from the opening created by colostomy, is sufficient to account for the delayed passage of barium sulfate through the colon after the administration of morphine (Krueger [14]).

The effect of atropine in decreasing the tone and the motility of the colon of man confirms the observations of Elsom and Drossner [17] and Jackman and Bargen.[16] This effect is further substantiated by the observation that on the average a dose of atropine sufficient to cause dryness of the mouth partially antagonizes the increase in tone and in nonpropulsive motility of the colon caused by morphine. This provides experimental justification for the simultaneous use of the two drugs for pain originating from the alimentary tract.

The fact that atropine and other antispasmodics we have used to date in reasonable doses (experiments in progress) do not completely abolish the hypertonus caused by morphine indicates to us the reason why none of them is completely satisfactory. In our opinion, the ideal antispasmodic is yet to be discovered. We suspect that when it is discovered, it will completely annul the increase in tone and in nonpropulsive activity induced by morphine.

SUMMARY AND CONCLUSIONS

Morphine sulfate in doses of 8, 10 and 16 mg. administered intramuscularly to a 140 pound (63.5 Kg.) healthy male patient who had undergone an ileostomy usually increased the tone and the amplitude of the nonpropulsive type of rhythmic contractions of the segments of the

16. Jackman, R. J., and Bargen, J. A.: The Influence of Certain Antispasmodic Drugs on the Intestine of Man, Surg., Gynec. & Obst. **67**:63, 1938.

17. Elsom, K. A., and Drossner, J. L.: Intubation Studies of the Human Small Intestine: XVII. The Effect of Atropine and Belladonna on the Motor Activity of the Small Intestine and Colon, Am. J. Digest. Dis. **6**:589, 1939.

distal portion of the ileum studied. The propulsive activity of the ileum was uniformly decreased; this was shown by the motility records and by the definite decrease in the amount of contents discharged into the ileostomy bag during a three hour period.

Dilaudid hydrochloride in doses of 1 or 2 mg. administered intramuscularly had a similar effect.

Morphine sulfate in doses of 8, 10 and 16 mg. administered intramuscularly to 4 healthy male patients who had undergone colostomy with resection of the proximal portion of the sigmoid and who weighed from 140 to 190 pounds (72.6 to 86.2 Kg.) usually increased the tone and the amplitude of the nonpropulsive type of rhythmic contractions of the segments of the descending colon studied. In all of 40 tests in which 5 to 16 mg. of the drug was given the propulsive motility of the descending colon was diminished or abolished. On 9 occasions in which the colon was manifesting diarrhea the administration of morphine abolished the discharge by decreasing the propulsive type of motility and not by reducing the tone and the quantity of motility the segments manifested.

Atropine sulfate in doses of 0.7 to 0.8 mg. administered intramuscularly to the 4 subjects just mentioned usually decreased the total motility of the portion of the colon being studied; the propulsive motility was uniformly diminished.

The administration of atropine sulfate (0.7 mg.) antagonizes partially that effect of morphine sulfate (8 mg.) which causes an increase in tone and in nonpropulsive motility. This evidence, we believe, supports the combined use of the drugs in the treatment of severe gastrointestinal pain. The failure of atropine in ordinary doses to antagonize completely the increase in tone and in nonpropulsive motility usually induced by morphine is interpreted as indicating why atropine is not always as effective an antispasmodic as is desired clinically.

Morphine sulfate delays the ileal and colonic passage time of material in man, primarily by interfering with or diminishing propulsive motility. We suggest that morphine causes dyskinesia of the small and large intestine. Adjacent segments of bowel must be coordinated in order that effective propulsion may occur.[7]

QUANTITATIVE STUDIES OF DIRECT-REACTING SERUM BILIRUBIN

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AND

G. HOLLANDER, M.D.

PHILADELPHIA

In the presence of hyperbilirubinemia little or no clinical significance is usually attached at the present time to the nature of the qualitative van den Bergh reaction, except in the diagnosis of hemolytic forms of jaundice. Its specificity even in this connection is rendered questionable by the recent reports by Dameshek and Singer [1] of instances of nonhemolytic familial jaundice (serum bilirubin values up to 13.1 mg. per hundred cubic centimeters) and by Malloy and Lowenstein [2] of apparently nonhemolytic hereditary jaundice in rats, only the indirect van den Bergh reaction having been obtained by these authors. Although the factors which determine the difference between the direct and the indirect reaction are not definitely known, it seems safe to assume for clinical purposes that bilirubin in the serum which does not give the direct reaction has not passed through the hepatic cells and that which does give this reaction has been reabsorbed into the blood from the bile canaliculi. This relation of the liver to the nature of the van den Bergh reaction was demonstrated clearly by Bollman and Mann,[3] who found in dogs that after cholecystectomy and ligation of the common bile duct practically all of the serum bilirubin was of the direct-reacting variety, increasing in amount with the time after operation. Subsequent hepatectomy, regardless of the level of serum bilirubin, was followed by a continued rise in the indirect-reacting serum bilirubin, but the direct-

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1. Dameshek, W., and Singer, K.: Familial Nonhemolytic Jaundice, Arch. Int. Med. **67**:259 (Feb.) 1941.

2. Malloy, H. T., and Lowenstein, L.: Hereditary Jaundice in Rat, Canad. M. A. J. **42**:122, 1940.

3. Bollman, J. L., and Mann, F. C.: Studies of the Physiology of the Liver: XXII. The van den Bergh Reaction in the Jaundice Following Complete Removal of the Liver, Arch. Surg. **24**:675 (Jan.) 1932.

reacting bilirubin remained at the same concentration it had reached as a result of the biliary obstruction and did not increase after removal of the liver.

Instances are occasionally observed clinically of mild grades of hyperbilirubinemia with a negative direct van den Bergh reaction in the absence of evidences of excessive hemolysis and, less frequently, of a positive direct reaction in the presence of a normal concentration of serum bilirubin. These phenomena occur most commonly in cases of nonobstructive cirrhosis, mild hepatitis and congestive heart failure and in the early stages of bile stasis and late stages of biliary decompression. Investigation of the absolute concentrations of direct-reacting and indirect-reacting bilirubin in the serum in such disorders has been hampered by the inaccuracy of hitherto available quantitative methods. The introduction, by Malloy and Evelyn,[4] of a photoelectric method for the exact determination of total and "direct" bilirubin has raised the possibility that some light might be thrown on the pathogenesis of these phenomena.

The present report consists of quantitative determinations of total (indirect-reacting) and direct-reacting serum bilirubin in 35 normal subjects, 94 patients with hepatitis (172 determinations), 14 with nonobstructive hepatic cirrhosis (41 determinations), 36 with extrahepatic biliary obstruction of varying degree (75 determinations), 11 with congestive heart failure and either hyperbilirubinemia or some other manifestation of impaired hepatic function (18 determinations) and 18 with hyperbilirubinemia due to other causes (40 determinations). Bilirubin was determined by the method of Malloy and Evelyn,[4] readings of "direct" bilirubin being made at thirty minutes in all cases and at five minutes in some cases. The latter (five minute) readings have been reported elsewhere[5] and, having been found to be of no added significance, will not be presented here.

RESULTS

The range of findings in each group of subjects in the series is presented in table 1.

Normal Subjects.—The concentration of serum bilirubin was 0.1 to 0.8 mg. per hundred cubic centimeters, the direct-reacting bilirubin constituting 0 to 75 per cent of the total bilirubin. As indicated in figure 1, it was absent in only 3 instances and was present in every case

4. Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481, 1937.

5. Cantarow, A.; Wirts, C. W., Jr., and Hollander, G.: Quantitative Studies of Direct Serum Bilirubin, Proc. Soc. Exper. Biol. & Med. **45**:253, 1940.

in which the concentration of total serum bilirubin exceeded 0.2 mg. per hundred cubic centimeters. With increasing values for the total serum bilirubin, the maximum percentage of the total represented by direct-reacting bilirubin diminished steadily from a peak of 75 per cent at 0.2 mg. per hundred cubic centimeters to 44 per cent at 0.8 mg. per hundred cubic centimeters.

Patients with Cirrhosis.—The individual values obtained in patients with cirrhosis are presented in figure 2. In all of 17 instances in this group in which the concentration of total serum bilirubin was within normal limits, the proportion of direct-reacting bilirubin (67 to 100 per

TABLE 1.—*Percentage of Direct-Reacting Bilirubin in the Serum at Different Levels of Total Serum Bilirubin*

	Direct-Reacting Bilirubin, 30 Min. Readings, %					
Total Bilirubin, Mg./100 Cc.	Normal	Cirrhosis	Hepatitis	Obstruction	Poisoning Caused by Sulfanilamide or One of Its Derivatives	Congestive Heart Failure
0.1	0-50	.....	.....	.....	.....	.....
0.2	0-75	.....	100	.....	.....	.....
0.3	33-67	.....	.....	.....	.....	.....
0.4	25-62	100	75	.....	50	.....
0.5	40-60	70-100	40-100	.....	.....	.....
0.6	33-50	67-83	83	.....	44	.....
0.7	36.50	.....	57-100	.....	.....	27
0.8	44	75-100	37-75	.....	62-75	.....
0.81- 1.0	.....	60-70	44-80	56	44-70	33-55
1.1 - 2.0	.....	33-86	25-100	38-75	33-79	30-64
2.1 - 5.0	.....	84-100	19-85	59-76	11-67	26-57
5.1 -10.0	.....	31-60	51-88	50-88	8-38	.....
10.1 -20.0	.....	.....	59-88	60-93	.....	.....
20.1 plus	.....	.....	84	66-92	.....	.....

cent) exceeded that present in normal subjects at the same level of total bilirubin (fig. 1). In the patients with hyperbilirubinemia, direct-reacting bilirubin comprised 60 per cent or more of the total in 19 of 24 instances.

Patients with Hepatitis.—The data on patients with hepatitis are presented in figure 3. In 19 of 23 instances in which the total serum bilirubin was within normal limits, the proportion of direct-reacting bilirubin exceeded that in normal subjects at the same level of total bilirubin (fig. 1). The degree of variation in the proportion of direct-reacting bilirubin lessened somewhat with increasing concentrations of total serum bilirubin, chiefly because of a gradual rise in the level of minimum values (table 1 and fig. 3). Direct-reacting bilirubin com-

prised 60 per cent or more of the total bilirubin in 35 of 53 instances (66 per cent) of concentrations of total serum bilirubin of 1.1 to 2.0 mg. per hundred cubic centimeters, in 32 of 50 instances (64 per cent) of concentrations of 2.1 to 5 mg. per hundred cubic centimeters, in 22 of

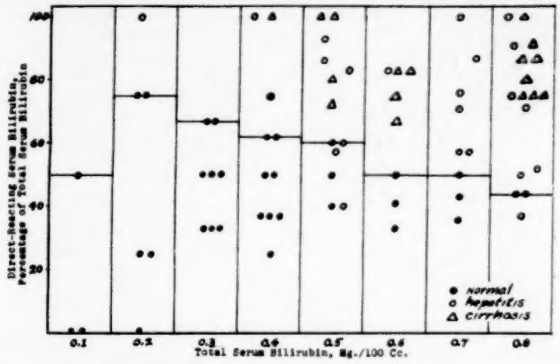

Fig. 1.—Proportion of direct-reacting serum bilirubin at normal levels of total serum bilirubin in normal subjects and in patients with hepatitis and with cirrhosis.

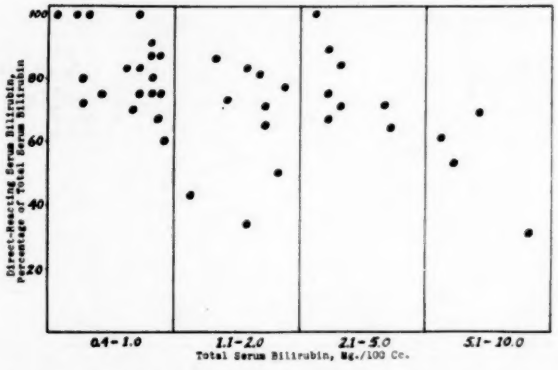

Fig. 2.—Proportion of direct-reacting bilirubin in the serum of patients with cirrhosis.

27 instances (81 per cent) of concentrations of 5.1 to 10 mg. per hundred cubic centimeters and in 14 of 15 instances (93 per cent) of concentrations above 10 mg. per hundred cubic centimeters.

Patients with Extrahepatic Obstruction.—The data on this group of patients, presented in detail in figure 4, were obtained during periods

of increasing, sustained and decreasing bile stasis, in the presence both of complete and of incomplete obstruction of the common bile duct. Direct-reacting bilirubin comprised 60 per cent or more of the total bilirubin in 3 of 7 instances (43 per cent) of concentrations of total

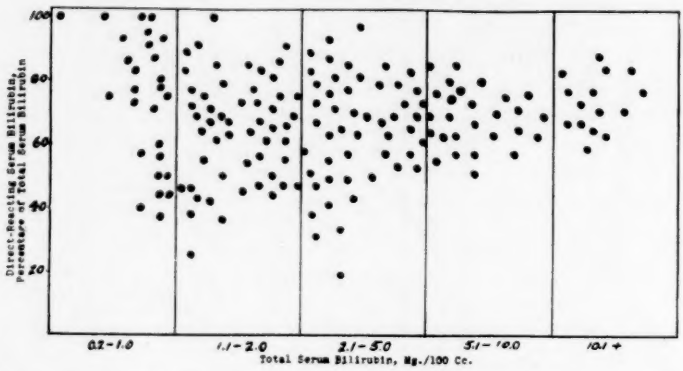

Fig. 3.—Proportion of direct-reacting bilirubin in the serum of patients with hepatitis.

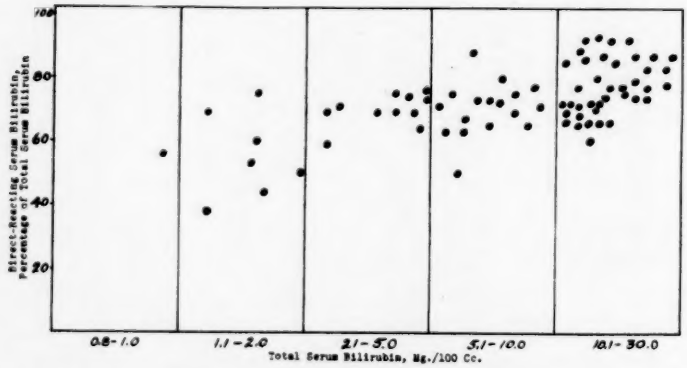

Fig. 4.—Proportion of direct-reacting bilirubin in the serum of patients with biliary obstruction.

serum bilirubin of 1.1 to 2 mg. per hundred cubic centimeters, in 10 of 11 instances (91 per cent) of concentrations of 2.1 to 5 mg. per hundred cubic centimeters, in 16 of 17 instances (94 per cent) of concentrations of 5.1 to 10 mg. per hundred cubic centimeters and in

all of 39 instances (100 per cent) of concentrations above 10 mg. per hundred cubic centimeters.

Patients with Congestive Heart Failure.—The data obtained on these patients are presented in figure 5. Hyperbilirubinemia (above 0.8 mg. per hundred cubic centimeters) was present in 17 of the 18 instances,

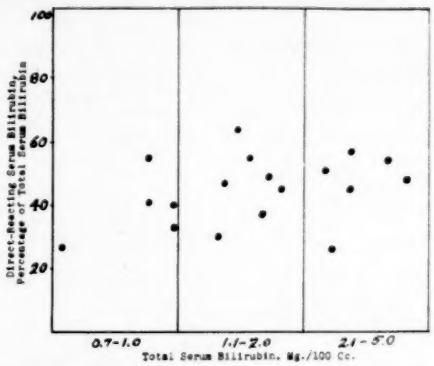

Fig. 5.—Proportion of direct-reacting bilirubin in the serum of patients with congestive heart failure and impairment of hepatic function.

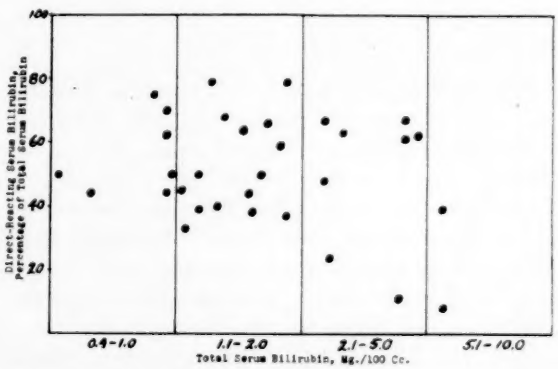

Fig. 6.—Proportion of direct-reacting bilirubin in the serum of patients following the administration of sulfanilamide or one of its derivatives.

and the proportion of direct-reacting bilirubin was above 60 per cent in only 1 case.

Patients Treated with Sulfanilamide or One of Its Derivatives.—The data obtained on patients in this group are presented in figure 6. Hyperbilirubinemia was present in 28 of the 32 determinations. The proportion

of direct-reacting bilirubin exceeded 60 per cent in 5 of 15 instances (33 per cent) of concentrations of total serum bilirubin of 1.1 to 2 mg. per hundred cubic centimeters, in 5 of 8 instances (62 per cent) of concentrations of 2.1 to 5 mg. per hundred cubic centimeters and in neither of 2 instances of concentrations above 5 mg. per hundred cubic centimeters. Serial data obtained on 1 patient are presented in table 2.

TABLE 2.—*Jaundice Following Treatment with Sulfanilamide*

	Days of Observation							
	1	3	4	5	6	8	10	12
Total serum bilirubin, mg./100 cc.	5.9	4.6	2.9	1.6	1.1	0.8	1.0	0.4
Direct-reacting bilirubin, 30 min. reading, mg./100 cc.	0.5	0.5	0.7	0.8	0.5	0.5	0.5	0.2
Direct van den Bergh reaction	—	—	+	+	+	+	+	—

Patients with Miscellaneous Conditions.—Data obtained on 5 patients with pernicious anemia are tabulated as follows:

Patient No.	Total Serum Bilirubin, Mg./100 Cc.	Direct-Reacting Serum Bilirubin, %
1	1.2	46
2	1.0	60
3	1.0	60
4	0.9	67
5	0.9	44

In 1 patient with massive hemorrhage from a duodenal ulcer the direct-reacting serum bilirubin comprised 33 per cent of the total of 0.9 mg. of bilirubin per hundred cubic centimeters of serum. In 2 patients with congenital hemolytic jaundice the direct-reacting serum bilirubin was 3 per cent of a total of 9.5 mg. per hundred cubic centimeters and 14 per cent of a total of 1.4 mg. per hundred cubic centimeters, respectively.

Direct-Reacting Bilirubin and Direct van den Bergh Reaction.—In the patients with cirrhosis, biliary obstruction and congestive heart failure, the direct van den Bergh reaction was negative in the presence of hyperbilirubinemia (above 0.8 mg. per hundred cubic centimeters) on 30 occasions and was positive in the presence of normal concentrations of total serum bilirubin in 17 instances. These data are presented in table 3. A negative direct van den Bergh reaction was obtained with concentrations of total serum bilirubin as high as 2.2 mg. per hundred cubic centimeters, the direct-reacting bilirubin being 0.6 mg. per hundred cubic centimeters, or 27 per cent of the total (hepatitis), and with concentrations of direct-reacting bilirubin as high as 1.1 mg. per hundred cubic centimeters, comprising 69 per cent of the total of 1.6 mg. per

hundred cubic centimeters (hepatitis). A positive direct van den Bergh reaction was obtained with concentrations of total serum bilirubin as low as 0.4 mg. per hundred cubic centimeters, all of which was direct-reacting bilirubin (cirrhosis) and with concentrations of direct-reacting bilirubin as low as 0.3 mg. per hundred cubic centimeters, comprising 37 per cent of the total of 0.8 mg. per hundred cubic centimeters (hepatitis).

TABLE 3.—*Relation of Qualitative van den Bergh Reaction to Amount and Proportion of Direct-Reacting Bilirubin in the Serum*

Direct van den Bergh Reaction	Total Serum Bilirubin, Mg./100 Cc.	Direct-Reacting Bilirubin, 30 Min. Reading							
		Hepatitis		Cirrhosis		Obstruction		Congestive Heart Failure	
		Mg./100 Cc.	%	Mg./100 Cc.	%	Mg./100 Cc.	%	Mg./100 Cc.	%
Positive	0.4	...	..	0.4	100	...	..	...	..
	0.5	...	..	0.5	100	...	..	...	..
	0.5	...	..	0.4	70	...	..	...	..
	0.6	0.5	83	0.4	67	...	..	...	..
	0.7	0.4	57	0.5	83	0.5	71	...	..
	0.7	0.6	86	...	...	0.5	71	...	..
	0.7	0.6	86	...	...	...	..	...	..
	0.8	0.3	37	0.6	75	0.8	100	...	..
	0.8	0.4	50	0.8	100	...	..	...	..
	0.8	0.6	75	...	...	...	..	...	..
Negative	0.9	0.4	44	...	...	0.5	56	0.3	33
	0.9	0.4	44	...	...	...	..	0.5	55
	0.9	0.7	78	...	...	...	..	...	..
	1.0	0.5	50	...	...	0.8	80	0.4	40
	1.0	0.5	50	...	...	...	..	...	..
	1.0	0.6	60	...	...	...	..	...	..
	1.1	0.4	36	...	...	...	..	...	..
	1.1	0.6	54	...	...	...	..	...	..
	1.2	0.3	25	0.8	67	...	..	...	..
	1.2	0.5	42	...	...	...	..	...	..
	1.2	0.5	42	...	...	...	..	...	..
	1.3	0.5	38	0.7	54	...	..	...	..
	1.3	0.6	46	...	...	...	..	...	..
	1.4	0.6	43	0.6	43	...	..	...	..
	1.4	0.7	50	...	...	...	..	...	..
	1.4	0.7	50	...	...	...	..	...	..
	1.5	0.7	47	...	...	0.8	53	...	..
	1.5	...	..	...	...	0.9	60	...	..
	1.6	1.1	69	0.9	56	...	..	...	..
	2.2	0.6	27	...	...	...	..	...	..

COMMENT

The data reported here for normal subjects are in essential agreement with the observation of Malloy and Evelyn [6] that "direct" bilirubin comprises about 35 to 70 per cent of the total serum bilirubin of normal adults. It appears, however, on the basis of a limited number of observations, that the proportion of the former decreases from a peak

6. Malloy, H. T., and Evelyn, K. A., cited by Waugh, T. R.; Merchant, F. T., and Maughan, G. B.: Blood Studies on the Newborn: II. Direct and Total Blood Bilirubin Determinations Over a Nine-Day Period, with Special Reference to Icterus Neonatorum, Am. J. M. Sc. **199**:9, 1940.

of 75 to about 44 per cent of the total at increasing levels of total bilirubin within normal limits (0.2 to 0.8 mg. per hundred cubic centimeters), the maximum concentration of "direct" bilirubin increasing simultaneously from 0.15 to 0.352 mg. per hundred cubic centimeters. The significance of the presence in normal serum of such relatively large quantities of bilirubin giving the van den Bergh reaction in aqueous acid (direct reaction) cannot be established because of the present uncertainty regarding the factors responsible for the difference in behavior of "direct" and of "indirect" bilirubin. It is obvious that production of the qualitative direct reaction, at least in serums of relatively low bilirubin content, is not determined by the concentration of direct-reacting bilirubin or by the proportion which it constitutes of the total. It must be remembered, however, that readings of the qualitative reaction are made at thirty seconds, while those of the quantitative reactions are made at thirty minutes, which may be responsible, in part at least, for this discrepancy. Nevertheless, it is difficult to explain a change such as that observed in a patient after administration of sulfanilamide (table 2), namely, the transition from a negative to a positive direct van den Bergh reaction at the same level of "direct" bilirubin (0.5 mg. per hundred cubic centimeters), with a decreasing concentration of total bilirubin (5.9 to 0.8 mg. per hundred cubic centimeters).

In the patients with pernicious anemia the "direct" bilirubin ranged from 0.396 to 0.603 mg. per hundred cubic centimeters at levels of total serum bilirubin of 0.9 to 1.2 mg. per hundred cubic centimeters, the direct van den Bergh reaction being negative in each instance. These figures represent an increase in the former above the maximum observed in normal subjects (0.352 mg. per hundred cubic centimeters) and are in rather striking contrast to the relatively low values obtained in a patient with gastrointestinal hemorrhage (0.307 mg.) and in patients with congenital hemolytic jaundice (0.285 and 0.196 mg.).

Hyperbilirubinemia, even of minimal degree, in the patients with cirrhosis, hepatitis, biliary obstruction and congestive heart failure and in patients treated with sulfanilamide or one of its derivatives was accompanied by an abnormally high level of "direct" bilirubin in all patients but 1 with hepatitis (0.3 mg.), 1 with congestive heart failure (0.33 mg.) and 1 with sulfanilamide poisoning (0.31 mg.). Of particular significance is the fact that at levels of serum bilirubin within normal limits the concentration of "direct" bilirubin was above the maximum observed in normal subjects in all of the patients with cirrhosis and in 19 of 23 patients with hepatitis. The highest value for non-direct-reacting bilirubin in normal subjects was 0.448 mg. per hundred cubic centimeters. In the patients with hyperbilirubinemia, concentrations above this level

were present in all but 6 with cirrhosis (0.0 to 0.437 mg.), in all but 1 with biliary obstruction, in all with congestive heart failure and in all but 3 with poisoning caused by sulfanilamide or one of its derivatives. It is interesting that, in contrast to these findings, in about one half of the patients with hepatitis with concentrations of total serum bilirubin of 1.1 to 2 mg. per hundred cubic centimeters the level of non-direct-reacting bilirubin was within the limits of normal. The percentage of such levels decreased sharply at higher degrees of bilirubinemia, and with concentrations of total serum bilirubin above 4 mg. per hundred cubic centimeters there was an elevation of the non-direct-reacting pigment in every instance.

If the view can be maintained that bilirubin in the blood that does not give the direct van den Bergh reaction has not passed through the hepatic cells, while that which does give the reaction has been reabsorbed from hepatic cells or from the bile canaliculi, these data furnish interesting information regarding the pathogenesis of hyperbilirubinemia in the conditions represented in this series of patients. In the great majority of cases the jaundice is apparently a combination of the "regurgitation" and the "retention" variety, as designated by Rich.[7] It appears, also, that the regurgitation mechanism frequently predominates in those patients with cirrhosis or hepatitis with normal or slightly increased bilirubinemia. In jaundice due to congestive heart failure or to poisoning caused by sulfanilamide or one of its derivatives the increase in "indirect" bilirubin may be contributed to by increased production (excessive hemolysis). Other data must be taken into consideration if the role of this factor is to be evaluated properly.[8] The observations presented here suggest that the quantitative determination of "direct" serum bilirubin may be of clinical value in detecting hepatic functional impairment in the presence of a normal concentration of total bilirubin. Values above the maximum obtained in normal subjects (0.352 mg. per hundred cubic centimeters) or proportions of the total greater than those observed at different levels of normal bilirubinemia (fig. 1) are commonly present in patients with cirrhosis or mild grades of hepatitis.

SUMMARY

Determinations were made of the concentration of total and of "direct" bilirubin in the serum of normal subjects and of patients with cirrhosis, hepatitis, biliary obstruction, congestive heart failure and poisoning caused by sulfanilamide or one of its derivatives. The serum

7. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338, 1930.

8. Kugel, M. A., and Lichtman, S. S.: Factors Causing Clinical Jaundice in Heart Disease, Arch. Int. Med. **52**:16 (July) 1933.

of normal subjects contained 0 to 0.352 mg. of "direct" bilirubin per hundred cubic centimeters, the maximum proportion of the total serum bilirubin being 75 per cent when the latter was 0.2 mg. per hundred cubic centimeters and decreasing steadily to 44 per cent at a concentration of total bilirubin of 0.8 mg. per hundred cubic centimeters.

Data are presented which indicate that jaundice in the great majority of patients with cirrhosis, hepatitis, biliary obstruction and congestive heart failure is a combination of the "regurgitation" and the "retention" variety. They also suggest that the quantitative determination of "direct" serum bilirubin may be of clinical value in detecting hepatic functional impairment in the presence of a normal concentration of total serum bilirubin, particularly in patients with cirrhosis or mild grades of hepatitis.

CARBOHYDRATE COMBUSTION IN HUMAN SUBJECTS AFTER ORAL AND AFTER INTRAVENOUS ADMINISTRATION OF DEXTROSE

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In some studies being carried on at the New England Deaconess Hospital on the metabolism of sugars in patients with diabetes mellitus, it has been observed occasionally that intravenous administration of dextrose is not followed by the expected rise in the respiratory quotient. As intravenous injection of dextrose is a common practice in medicine, particularly after surgical procedures, it was considered worth while to make a comparative study of the changes in the respiratory quotient and in the total metabolic rate of normal human subjects after oral ingestion and after intravenous administration of this sugar.

In 2 fasting rabbits given intravenous injections of dextrose (10 cc. of a 13 per cent solution in thirteen minutes and 50 cc. of a solution containing 6 Gm.—rate of injection not stated) Zuntz and von Mering [1] noted marked increases in the respiratory quotient. In another fasting rabbit, given by stomach tube 20 Gm. of dextrose in 80 cc. of water, they also observed an increase in the quotient. In a rabbit which had fasted twenty-two hours Wolfers [2] noted that an intravenous injection of a 5 per cent solution of dextrose (amount and rate not given) failed to cause an increase in the respiratory quotient, which he ascribed to the fact that the rabbit still had a good supply of carbohydrate in the body and hence a high initial quotient. In another rabbit, which had fasted forty-eight hours, he found that intravenous injection of a 5 per cent solution of dextrose (0.272 Gm. per fifteen minutes for one and three-quarters hours) caused an increase in the respiratory quotient.

A preliminary report of this study was presented before the American Institute of Nutrition, New Orleans, March 13, 1940 (J. Nutrition [supp.] **19**:10, 1940).

From the George F. Baker Clinic (Dr. Elliott P. Joslin, Medical Director), New England Deaconess Hospital, and the Nutrition Laboratory, Carnegie Institution of Washington.

1. Zuntz and von Mering: Inwiefern beeinflusst Nahrungszufuhr die thierischen Oxydationsprocesse? Arch. f. d. ges. Physiol. **32**:173-221, 1883.

2. Wolfers, J.: Untersuchungen über den Einfluss einiger stickstofffreier Substanzen, speciell des Alkohols, auf den thierischen Stoffwechsel, Arch. f. d. ges. Physiol. **32**:222-279, 1883.

Laulanié [3] reported increases in the respiratory quotients of 2 fasting dogs given 10, 36 and 50 Gm. of dextrose intravenously in thirty minutes, ten minutes and one hour, respectively. After intravenous injection of dextrose at rates ranging from 1 to 9 Gm. per kilogram per hour and for periods lasting in some instances two to eight hours, increases in the respiratory quotients of dogs were also noted by Harley,[4] Woodyatt,[5] Boyd and associates,[6] Hines and co-workers,[7] Wierzuchowski [8] and Wierzuchowski and Sekuracki.[9] On the other hand, Wierzuchowski and Borkowski [10] observed a decrease in the respiratory quotient after the administration of dextrose by vein. Three human subjects (2 normal and 1 abnormal) studied by Bernstein and Falta [11] showed distinct rises in the respiratory quotient after intravenous injection of 30 or 35 Gm. of dextrose in 300 or 500 cc. of water (rate not given); their glycogen stores had been previously depleted. Koster and associates [12] and Collens and co-workers [13] reported that after intra-

3. Laulanié, F.: Des renseignements fournis par les échanges respiratoires sur la destination immédiate des hydrates de carbone, Arch. de physiol. **28**:791-802, 1896.

4. Harley, V.: Influence du sucre en circulation sur les gaz de la respiration et sur la chaleur animale, Arch. ital. de biol. **21**:173-189, 1894.

5. Woodyatt, R. T.: Studies on Intermediate Carbohydrate Metabolism, in Harvey Lectures, 1915-1916, Philadelphia, J. B. Lippincott Company, 1916, pp. 326-345.

6. Boyd, J. D.; Hines, H. M., and Leese, C. E.: Study of Response to Continuous Intravenous Injection of Large Amounts of Glucose, Am. J. Physiol. **74**: 656-673 (Nov.) 1925.

7. Hines, H. M.; Boyd, J. D., and Leese, C. E.: The Effect of Fasting upon Certain Phases of Carbohydrate Metabolism, Am. J. Physiol. **88**:240-244 (March) 1929.

8. Wierzuchowski, M.: Intermediärer Kohlenhydratstoffwechsel: VIII. Mitteilung. Respiratorischer Gaswechsel der Glykose, Fructose und Galaktose bei ihrer intravenösen Injektion, Biochem. Ztschr. **230**:187-224, 1931; Oxidation of Glucose as Function of Its Supply, J. Physiol. **90**:440-464 (Sept.) 1937; The Origin and Limits of the Specific Dynamic Action of Intravenous Glucose, ibid. **91**:140-171 (Nov.) 1937.

9. Wierzuchowski, M., and Sekuracki, F.: Spaltungs-, Oxydations- und Energieumsatz beim Hunde: I. Mitteilung. Bildung und Beseitigung der Milchsäure in den Organen beim Hungern, sowie während der Oxydation von Galaktose, Glucose und Maltose, Biochem. Ztschr. **276**:91-111, 1935.

10. Wierzuchowski, M., and Borkowski, Z.: Differentiation of the Forms of Glucose Intoxication, Acta biol. exper. **12**:168-173, 1938; abstracted, Biol. Abstr. **13**:14539, 1939.

11. Bernstein, S., and Falta, W.: Respiratorischer Stoffwechsel und Blutzuckerregulation, Deutsches Arch. f. klin. Med. **125**:233-283, 1918.

12. Koster, H.; Goldzieher, M.; Collens, W. S., and Gerber, I. E.: Studies on Lactic Acid in the Blood: I. The Effect of Glucose and Insulin, J. Lab. & Clin. Med. **15**:723-726 (May) 1930.

13. Collens, W. S.; Goldzieher, M., and Koster, H.: Untersuchungen zur Wirkungsweise intravenöser Traubenzuckerinjektionen, Klin. Wchnschr. **10**:582-586 (March 28) 1931.

venous injection of 250 cc. of dextrose in a 20 per cent solution there were increases in the respiratory quotients of nondiabetic patients before operation but no increase or only a slight increase in the quotients of such patients during the first week following operation, after which there was a marked increase. Jahn [14] gave 50 Gm. of dextrose in 200 cc. of water both by mouth and intravenously to a normal and a diabetic subject. After oral administration the respiratory quotient of the normal subject increased; unfortunately, the course of the quotient after the intravenous injection was not reported. In the diabetic subject the respiratory quotient decreased after administration of dextrose by both methods. Pijoan and Gibson [15] gave normal human subjects 50 cc. of a 50 per cent dextrose solution intravenously and observed insignificant increases in the respiratory quotient. Examination of the literature failed to reveal any observations on the same normal human subject in which the effects on the respiratory quotient of oral and of intravenous administration of dextrose were compared.

METHOD

Four normal men, students of a nearby university, were used as subjects. The respiratory exchange was measured with an open circuit helmet apparatus involving gas analysis.[16] The gas analysis apparatus was standardized during the two months' period of study by nine analyses of outdoor air, which gave an average value for carbon dioxide content of 0.033 per cent, with a standard deviation of 0.0015 and an average value for oxygen content of 20.938 per cent, with a standard deviation of 0.0043. In four alcohol control tests the apparatus showed respiratory quotients of 0.661, 0.662, 0.670 and 0.674. The respiratory exchange was measured for three consecutive ten minute base line periods after the usual half hour of rest, with the subject sitting, postabsorptive. The sugar was then given orally or intravenously, according to the program, and the exchange was measured for nine consecutive fifteen minute periods after the administration of the sugar. When the dextrose was taken by mouth, 50 Gm. was given in 300 cc. of water, and an additional 50 cc. of water was used for a rinse. The temperatures of the doses varied from 9.5 to 18.5 C. The subject drank the solution within three to ten minutes, and about fifteen to twenty minutes after he finished, the first period of measurement following ingestion of the sugar began. When the sugar was administered intravenously, 50 Gm. was given in 500 cc. of physiologic solution of sodium chloride. The injection, in an antecubital vein, began four to nine minutes before the first period of measurement after the sugar was given. The duration of injection was about twenty to twenty-eight minutes; hence the injection did not end until sometime during the second period of measurement following administra-

14. Jahn, D.: Ueber die Beeinflussung des Energiestoffwechsels durch vegetative Reaktionen, Deutsches Arch. f. klin. Med. **166**:257-302, 1930.

15. Pijoan, M., and Gibson, J. G., II: The Rate of Disappearance of Intravenously Administered Dextrose in the Human Subject, Am. J. Physiol. **121**:534-536 (Feb.) 1938.

16. The observations on respiratory exchange were conducted by Basil James, with the assistance of George Lee in the gas analyses. The intravenous injections were made by Miss Dorothy V. Blanchard, R.N.

tion of the sugar. With 3 of the subjects 2 experiments with each method were made, and with 1 subject, 3 with each method. Samples of blood, from capillaries or from a vein, were taken in the postabsorptive period and one-half hour, one hour and two or two and one-half hours after the sugar was given.

RESULTS

The results of the measurements of respiratory exchange (respiratory quotient and oxygen absorption) are shown graphically in figures 1 to 4. In P. D. S. the base line respiratory quotient before oral ingestion was in both cases lower than the base line respiratory quotient before intravenous injection. The respiratory quotient rose markedly after oral and also after intravenous administration. The oxygen absorption

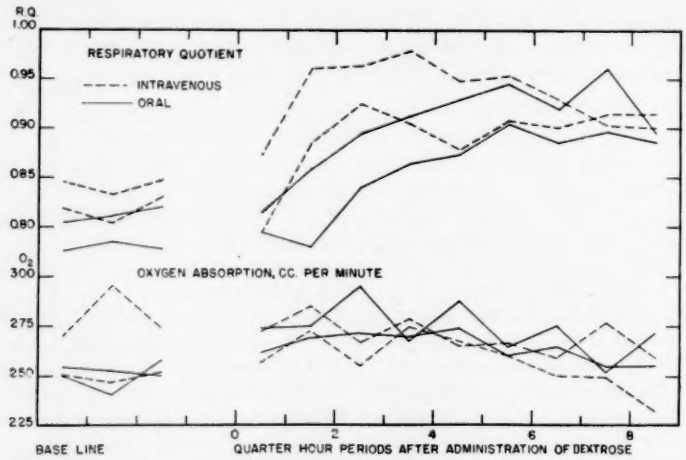

Fig. 1 (P. D. S.).—Respiratory exchange before and after oral and before and after intravenous administration of 50 Gm. of dextrose.

per minute was higher than the base line level for most of the two hours after oral ingestion. One of the base line oxygen values before intravenous injection was high and probably cannot be considered a true base line. If the other is accepted as correct, it would seem that the intravenous injection produced a rise in oxygen absorption in both series of experiments, which continued for at least two hours. Similarly in H. M. the respiratory quotients after the administration of sugar showed rises in both series of experiments and, for the most part, of about the same order of magnitude. The oxygen absorption after oral ingestion was raised, and after intravenous injection it was decidedly raised in 1 experiment but not in the other. In R. C. the respiratory quotient was raised after the administration of sugar in both series of experiments.

The oxygen absorption was higher after oral ingestion, but after intravenous injection there was, in 2 of the 3 experiments, little, if any, indication of a rise. In E. B. M. there was a marked rise both in the

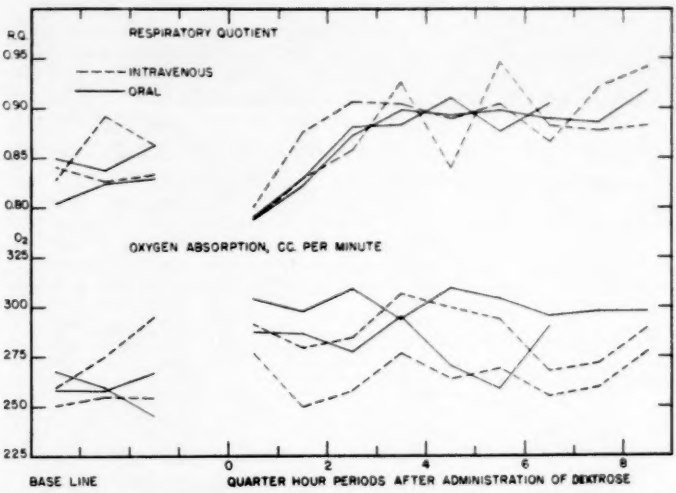

Fig. 2 (H. M.).—Respiratory exchange before and after oral and before and after intravenous administration of 50 Gm. of dextrose.

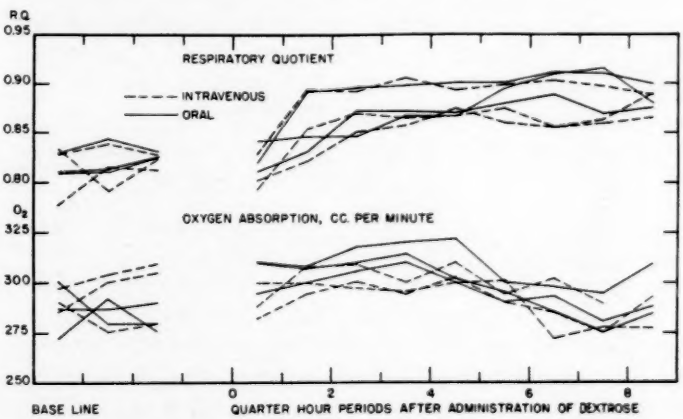

Fig. 3 (R. C.).—Respiratory exchange before and after oral and before and after intravenous administration of 50 Gm. of dextrose.

respiratory quotient and in oxygen absorption in both series of experiments. Considered graphically, the data do not show a marked difference between the changes either in the respiratory quotient or in oxygen

absorption after oral and after intravenous administration of 50 Gm. of dextrose.

Table 1 shows the effects of the method of administration of dextrose on the blood sugar and the urinary sugar. The base line values for

TABLE 1.—*Effect on the Sugar in the Blood and in the Urine of Normal Men of Oral and of Intravenous Administration of Fifty Grams of Dextrose*

Subject	Age, Yr.	Weight,* Kg.	Height, Cm.	Route of Administration	No. of Experiments	Sugar in Blood, %				Sugar in Urine, Gm.
						Base Line	After Dextrose ½ Hr.	After Dextrose 1 Hr.	After Dextrose 2 to 2½ Hr.	
P. D. S.	23	77.0	177	Oral.....	2	0.09	0.14	0.14	0.07	0.1
				Intravenous	1	0.10	0.18	0.11	0.07	1.6
H. M.	22	77.4	178	Oral.....	1	0.09	0.13	0.13	0.07	0.0
				Intravenous	1	0.08	0.18	0.10	0.10	3.6
R. C.	21	79.0	181	Oral.....	2	0.11	0.15	0.15	0.08	0.1
				Intravenous	3	0.10	0.19	0.12	0.08	2.7
E. B. M.	23	69.8	175	Oral.....	1	0.09	0.12	0.10	0.08	0.0
				Intravenous	1	0.08	0.11	0.08	0.07	2.7
Average.....				Oral.....	..	0.09	0.14	0.13	0.08	0.0
				Intravenous	..	0.09	0.17	0.10	0.08	2.7

* Without clothes.

TABLE 2.—*Increases in Heat Production and in Carbohydrate Combustion in Normal Men During Two and One-Quarter Hours After Oral and After Intravenous Administration of Fifty Grams of Dextrose*

Subject	Route of Administration	No. of Experiments	Heat Production, Calories				Carbohydrate Combustion, Gm.			
			Base Line	Increase Above Base Line Range	Increase Above Base Line Average	Average Difference	Base Line	Increase Above Base Line Range	Increase Above Base Line Average	Average Difference
P. D. S.	Oral.....	2	160.4	13.1-18.4	15.7		9.1	11.8-15.0	13.4	
	Intravenous	2	160.0	8.4-18.7	13.6	— 2.1	13.2	11.1-15.8	13.4	±0.0
H. M.	Oral.....	2	167.7	17.7-27.5	22.6		15.2	7.1- 9.0	8.0	
	Intravenous	2	171.3	8.6- 9.7	9.2	—13.4	17.0	5.5- 6.2	5.9	—2.1
R. C.	Oral.....	3	183.7	8.0-17.1	13.3		15.2	9.1-10.5	9.9	
	Intravenous	3	182.1	6.8-14.4	9.8	— 3.5	14.1	6.9- 9.8	8.4	—1.5
E. B. M.	Oral.....	2	161.3	15.1-19.5	17.3		17.4	9.7-12.3	11.0	
	Intravenous	2	161.3	16.2-16.7	16.4	— 0.9	16.1	7.7- 8.7	8.2	—2.8
Average	Oral.....	..	.....	.....	17.2		....	.....	10.6	
	Intravenous	..	.....	.....	12.3	— 5.0	....	.....	9.0	—1.6

blood sugar lie within a narrow range and are normal. One-half hour after administration of sugar the blood sugar was in all subjects with the exception of E. B. M. higher after intravenous injection than after oral ingestion and above the threshold for escape of urinary sugar. At one hour after intravenous injection, on the contrary, the blood sugar was in all cases lower than one hour after oral ingestion. There was no significant difference in the values at two to two and a half hours. In

all the observations with intravenous injection there was an elimination of sugar in the urine, varying from 1.6 Gm. in P. D. S. to 3.6 Gm. in H. M. After oral ingestion there was a trace of sugar in the urine in 2 subjects.

The increases in heat production after the administration of sugar are summarized in table 2. The ranges in the increases are wide for most of the groups of experiments, but on the whole the oral ingestion resulted in a greater increase in heat production than the intravenous injection. This was most marked in H. M. and least marked in E. B. M.

The increases in carbohydrate combustion are also summarized in table 2. In P. D. S. the method of administration of sugar made no

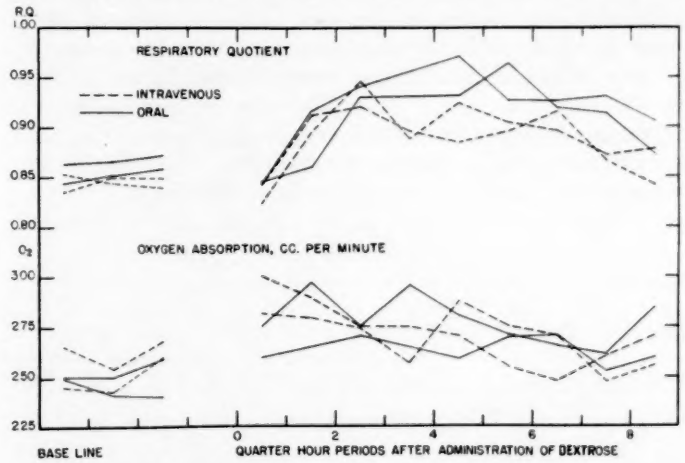

Fig. 4 (E. B. M.).—Respiratory exchange before and after oral and before and after intravenous administration of 50 Gm. of dextrose.

difference, on the average, in the increase in carbohydrate combustion. The other 3 subjects showed a slightly lower carbohydrate combustion after intravenous injection than after oral ingestion, the differences ranging from 1.5 to 2.8 Gm. In the main, these correspond closely to the differences between the elimination of sugar in the urine in the comparison of oral and of intravenous administration shown in table 1. The observations lasted only two and one-quarter hours after the administration of the sugar, and it is probable that this period was not long enough to include all the increases in carbohydrate combustion. Therefore, this good comparison between differences in carbohydrate combustion and in elimination of sugar in the urine may be more apparent than real.

The results indicate that in these normal men for two and one-quarter hours after the administration of 50 Gm. of dextrose the rises in respiratory quotient were practically the same whether the sugar was given by mouth or by vein, and consequently there was little difference in the carbohydrate combustion. The oral ingestion gave an insignificantly higher carbohydrate combustion and a greater increase in heat production than did the intravenous injection, whereas the latter method of administration resulted in a more definite elimination of sugar in the urine, there being practically no such elimination after oral ingestion.

SUMMARY

In 4 normal men the blood sugar was higher one-half hour after and lower one hour after intravenous injection of 50 Gm. of dextrose than it was at the same times after oral ingestion of the same amount, but there was no difference in the values after two to two and one-half hours. Sugar was eliminated in the urine only after intravenous injection. The increases in respiratory quotient, heat production and carbohydrate combustion above the postabsorptive base lines were insignificantly greater after oral than after intravenous administration.

BLOOD PYRUVIC ACID IN HEART DISEASE

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Meakins and Long [1] were the first to study intermediates of tissue carbohydrate metabolism in heart disease. In 1927 they showed a marked and proportional increase in blood lactic acid in patients with heart failure. The validity of these results was subsequently both confirmed [2] and denied.[3] The importance of lactic acid as the center of carbohydrate metabolism has since been overshadowed by that of pyruvic acid, and recently even more interest has attached itself to pyruvic acid because of Peters' [4] discovery that the presence of vitamin B_1 is necessary for its oxidation.

In 1937 Taylor, Weiss and Wilkins [5] attempted estimations of blood pyruvic acid on persons with all types of disease by measuring the blood bisulfite–binding substances and showed a rise of these in subjects with failing hearts. This method of pyruvate estimation has since been shown, however, to be nonspecific and inaccurate.[6] This present work makes use of the specific method of Lu [7] and deals only with heart disease.

From the Lasker Foundation for Medical Research and the Department of Medicine of the University of Chicago.

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2. Harris, I.; Jones, E. W., and Aldred, C. N.: Blood p_H and Lactic Acid in Different Types of Heart Disease, Quart. J. Med. **4**:407 (Oct.) 1935.

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7. Lu, G. D.: Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B_1 Deficient States: I. A Rapid Specific and Sensitive Method for the Estimation of Blood Pyruvate, Biochem. J. **33**:249 (Feb.) 1939.

METHOD

The levels of pyruvate in the blood of organically normal subjects and patients with decompensated and with compensated heart disease were studied. The control group consisted of 5 male and 5 female subjects with psychopathic disorders, all carefully selected, ranging in age from 25 to 84; none of them was addicted to alcohol, had any evidence of organic disease or dietary deficiency or was excited or depressed. A pyruvate determination was done on each subject daily for six days and after one-half hour of rest in bed. Twenty hospital patients aged 32 to 79 with varying degrees of congestive failure and with no fever, history of dietary deficiency or impaired renal function other than that due to the cardiac failure and no other organic disease constituted the second group on whom daily determinations of blood pyruvate were made. In the third group were 12 patients aged 20 to 62 with heart disease but without failure; single determinations were done on these patients.

RESULTS AND COMMENT

The values for blood pyruvic acid obtained in 60 determinations on the physically normal group (table 1) varied between 0.56 and 1.1 mg.

TABLE 1.—*Range and Mean Levels of Pyruvate in the Blood of Controls*

Subject No.	Blood Pyruvate, Mg./100 Cc.	
	Range*	Mean
24	0.5-0.8	0.68
25	0.7-0.8	0.76
26	0.8-1.0	0.92
27	0.8-1.0	0.92
28	0.8-1.0	0.88
29	0.6-0.9	0.76
30	0.6-0.9	0.79
31	0.6-1.1	0.88
33	0.6-0.9	0.73
34	0.6-1.0	0.80

* The range is based on six daily determinations.

per hundred cubic centimeters, with a mean of 0.8 mg. Only one value was above 1.0 mg.

The maximum blood pyruvate was significantly elevated in all of the patients with decompensated heart disease except 1 (table 2). The mean "peak" rise for the group was 2.15, with a range of 1.2 to 3.4 mg. per hundred cubic centimeters.[8]

The blood pyruvate curve of each patient in failure was generally in accord with his clinical course (table 3). The 4 patients who left the hospital with hearts compensated (5, 15, 17 and 20) had normal values at the end of their stay in the hospital. Three patients (6, 12 and 18) were discharged with hearts still slightly decompensated. Their terminal levels of blood pyruvate were at the upper limits of normal. Two patients

8. This roughly approximates the values that Platt and Lu (Chemical and Clinical Findings in Beriberi with Special Reference to Vitamin B_1 Deficiency, Quart. J. Med. **29**:355 [July] 1936) obtained on subjects with acute beriberi.

who left the hospital with hearts decompensated (1 and 8) had continuously high levels of pyruvate during their entire hospital stay. The 2 patients (4 and 19) who remained refractory to treatment during this study also showed constantly elevated levels of pyruvate.

Every patient but 1 showed changes from day to day. These variations, however, were not considered significant unless they were higher than 0.3 mg. per hundred cubic centimeters, the maximum day to day variation of the controls. An attempt was made to correlate the daily fluctuation with the clinical condition on the same day. If one allows for one discordant variation, 80 per cent of the patients showed daily

TABLE 2.—*Highest Level of Pyruvate (Peak) in the Blood of Patients with Decompensated Heart Disease*

Subject No.	Type of Heart Disease*	Severity of Condition*	Peak, Mg./100 Cc.
1	H	S	3.4
2	H	S	1.9
3	A	S	2.0
4	A	M	2.2
5	A	M	1.8
6	A	M	2.0
7	A	S	2.3
8	H	M	1.8
10	A	S	1.9
11	H	S	2.2
14	A	S	2.1
15	R	M	1.4
17	R	M	1.2
18	U	M	1.7
19	H	S	2.5
20	R	M	1.5
21	H	S	1.7
22	CT	S	1.7
47	A	M	1.5
49	R	S	1.8

* The following abbreviations have been employed: H, hypertension; A, arteriosclerosis; R, rheumatic heart disease; CT, coronary thrombosis; U, unknown; S, severe, and M, moderate.

variations in agreement with the corresponding clinical changes. Or of a sum total of fifty-eight daily variations in all of the patients, 43, or 74 per cent, were clinically correlative.

It should be remembered, however, that clinical estimation of the day to day change of the condition of a patient with heart disease is difficult, if not at times impossible. It is quite possible, therefore, that even though a given daily level of pyruvate does not fit in with the clinical evaluation of that day the former may still be the better criterion of the patient's true condition. That the mean peak of pyruvate in the blood of patients with severe failure was 2.13 mg. per hundred cubic centimeters as contrasted with 1.67 mg. for those moderately ill may be further evidence in this direction.

Of the 7 patients who died, 3 showed a rise of blood pyruvate as death approached, 3 no change and 1 a fall. It is interesting to note

TABLE 3.—*Daily Levels of Pyruvate in the Blood of Patients with Decompensated Heart Disease*

Subject No.*	Blood Pyruvate, Mg./100 Cc., and Clinical Condition†											Comment
1.....	2.3	1.9 I	3.4 S	2.1 I	1.8 I	1.5 S	1.2 S	1.4 S	1.5 S	1.7‡ W		Left hospital with heart decompensated
2.....	1.9	1.3 I	1.6 W	1.5 S	Died							Critically ill on entrance
3.....	1.4	1.4 S	1.8 S	0.9 S	0.8 I	1.4 S	0.9 I	1.0 S	1.3 W	1.5 W	2.0 W	Died Progressed satisfactorily for 8 days; became semicomatose on 9th day
4.....	0.9	2.2 I	1.6 I	1.1 W	0.9 S	1.4 W	0.9 S	1.7 S	1.5 S	1.5 S	1.2 W	2.0 I 1.5 S Refractory to treatment; remained in hospital
5.....	1.8	1.3 I	1.5 I	0.9 I	0.7 I	0.5 I	0.9 S	0.7 S	0.7 S	1.2 S	0.6 S	0.7 S Discharged with heart compensated
6.....	1.8	1.9 S	2.0 S	1.0 I	1.5 S	1.2 I	1.2 I	0.9 I	1.0 W	1.5‡ W		Discharged with slight decompensation
7.....	1.4	2.0 W	2.3 W	Died								Suddenly became critically ill on 3rd day
8.....	1.7	1.7 I	1.8 I	1.2 I	1.4 S	0.8 I	1.3 W	0.9 I	1.4 W	1.5 S	1.8 W	1.7 S Heart never compensated; discharged
10.....	0.8	0.8 I	1.5 W	1.9 S	1.5 W	1.4 W	Died					Severely ill on entrance; became critically ill on 3rd day
12.....	2.2	1.8 I	1.6 S	1.6 I	1.2 I	1.5 S	1.7 S	1.0 W	1.0 S	1.4‡ W		Discharged with slight decompensation
14.....	2.1	1.4 W	1.5 S	1.5 S	1.9 W	Died						Severely ill on entrance
15.....	1.4	1.4 S	1.2 I	1.3 I	0.7 I	1.4 W	0.9 I	0.9 S				Discharged with heart compensated
17.....	1.0	1.2 S	1.1 I	0.8 I	0.7 I	0.9 I						Discharged with heart compensated
18.....	1.4	1.2 S	1.1 I	1.7 W	1.7 S	5.0§ W	0.9 I	1.5 S	1.1 I			Heart almost compensated on last day
19.....	1.8	1.5 S	1.6 S	1.6 S	1.5 S	1.5 S	1.7 S	1.6 S	1.6 S	2.5 W		Remained refractory to treatment; died later
20.....	1.5	1.2 I	1.4 S	1.0 I	1.5 W	1.2 I	1.1 I	1.0 I	0.8 I	0.8 I		Discharged with heart compensated
21.....	1.7	1.5 W	Died									Entered critically ill
22.....	1.7	1.5 W	Died									Entered critically ill

* For the type of heart disease see table 2.
† The following abbreviations have been employed: I, improved; S, same, and W, worse.
‡ This value for blood pyruvate was obtained at home after the patient left the hospital. In all cases the patients were definitely clinically worse at home.
§ Patient got out of bed without permission.

TABLE 4.—*Level of Pyruvate in the Blood of Patients with Compensated Heart Disease*

Subject No.	Type of Heart Disease*	Blood Pyruvate, Mg./100 Cc.
35.....	R	0.8
36.....	R	0.6
37.....	A	0.8
38.....	A	0.6
39.....	A	0.7
41.....	R	0.8
43.....	H	0.9
44.....	H	0.8
53.....	H	0.6
54.....	H	0.7
55.....	H	1.1
56.....	A	0.8

* The following abbreviations have been employed: R, rheumatic; A, arteriosclerotic, and H, hypertensive.

that in 2 patients with edema of noncardiac origin which were also studied the blood pyruvate showed no rise above the normal level at any time.

Patients 4, 8 and 10 had "high normal" values on two occasions each, even though their hearts remained constantly decompensated. In patient 4 this occurred only twice in a total of thirteen determinations; in patient 12, twice in a total of twelve determinations, and in patient 10, twice in a total of six determinations. I have no explanation for these few divergent values.

Two patients with heart disease and with serous effusions were studied (patients 47 and 49, table 2). The blood of 1 contained 1.5 mg. of pyruvate per hundred cubic centimeters at a time when the pleural fluid contained 1.4 mg. per hundred cubic centimeters. The blood pyruvate of the second patient was 1.6 mg. per hundred cubic centimeters, with the pyruvate concentration of the ascitic fluid 2.7 mg. per hundred cubic centimeters.

For the group with compensated hearts (table 4) 12 patients with definite cardiac enlargement (10 to 110 per cent oversized) were selected for study. It is significant that the pyruvate levels were well within normal limits. Of further interest were 2 ambulatory patients with heart disease in whom compensation appeared to be complete except for a definite but slight edema, and they both had increased values of 1.2 mg. of pyruvate per hundred cubic centimeters of blood.

The answer to the question of why blood pyruvic acid increases in persons with heart failure can only be one of speculation. Increased utilization of dextrose and its intermediates may occur and might explain the accumulation of pyruvic acid in the blood. A second possibility is that the anoxia of the failing circulation may prevent the oxidation of pyruvic acid and hence contribute to its accumulation. Circulatory sluggishness or mechanical impediment to the removal of the excess pyruvic acid from the blood may also play a role.

It is conceivable that serial estimations of the pyruvic acid in the blood of patients with heart disease might prove valuable in following the course of the disorder.

CONCLUSIONS

1. There is a rise above normal of pyruvic acid in the blood of persons with heart failure.

2. This elevation approximates the degree of failure.

Dr. Emmet B. Bay contributed helpful suggestions and criticisms, and Dr. E. S. G. Barron permitted me the use of his laboratory and gave technical guidance.

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EFFECT OF UNDERNUTRITION ON CARDIAC OUTPUT AND CARDIAC WORK IN OVERWEIGHT SUBJECTS

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The purpose of this study is to demonstrate the beneficial effect of undernutrition and reduction in weight on the heart and circulation. The influence of a low calory diet on pulse rate, blood pressure, oxygen consumption, arteriovenous oxygen difference and cardiac output was determined over a long period in normal overweight subjects.

In obesity the heart functions under two handicaps. In the first place, the increased surface area results in an absolute rise in total body metabolism and oxygen consumption, which augments the work of the heart. Secondly, the elevated diaphragm limits the respiratory movements and compresses the lungs, causing a reduction in vital capacity. Both of these factors place a burden on the heart and explain the tendency of obese persons to fatigue and to dyspnea on mild effort, indicative of diminished exercise tolerance.

In studies on dietary restriction in subjects of normal weight Benedict and his co-workers [1] observed a drop in oxygen consumption, basal metabolic rate, pulse rate and blood pressure. Master and his co-workers [2] demonstrated similar changes in patients with acute and

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with chronic coronary artery disease and emphasized the beneficial effects of undernutrition in these conditions as well as in heart failure. In addition to the aforementioned effects on the circulation, Proger and Magendantz [3] observed also a decrease in cardiac output in patients with congestive heart failure on prolonged dietary restriction. Roemheld,[4] investigating the effect of restriction of fluids and salt as well as caloric intake on normal subjects and on patients with cardiac disease, found that after three to five days the cardiac output showed an average drop of 0.25 liter per minute. However, the results pertaining to the low calory diet (980 calories daily for three days) were inconclusive, since the changes were within physiologic limits of variation and since the period of observation was too short.

MATERIAL AND METHOD

Our observations were made on 5 overweight subjects whose ages ranged from 15 to 50 years and whose actual weight exceeded the ideal weight by 19 to 30 per cent. They were placed on a 1,200 calory diet; they remained ambulatory and continued to perform their usual activities. We made cardiac output determinations once or twice weekly for several months, using the three sample modification of the Grollman acetylene method.[5] All the determinations were made before breakfast with the subjects in the basal state, in the semirecumbent position. We checked our results by the Wetzler-Boeger method [6] based on physical principles; the cardiac output is calculated by determining the pulse wave velocity, the pulse pressure and the diameter of the aorta. Results of comparative determinations employing both methods checked within 10 per cent. The cardiac work was computed in kilogram-meters per minute, according to the formula work $= Q \times R + \frac{MV^2}{2}$.[7]

RESULTS

The results are summarized in the table. It will be seen that the average loss of weight was 12 per cent of the initial weight. This was

3. Proger, S. H., and Magendantz, H.: Effect of Prolonged Dietary Restriction on Patients with Cardiac Failure, Arch. Int. Med. **58**:703 (Oct.) 1936.

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6. Wetzler, K., and Boeger, L.: Die Dynamik des arteriellen Systems, Ergebn. d. Physiol. **41**:1, 1939.

7. Q = cardiac output; R = peripheral resistance as measured by the mean arterial pressure; M = mass of stroke output; V = blood velocity. The factor $\frac{MV^2}{2}$ is normally 0.7 gram-meter per stroke and as a rule is negligible (Wiggers, C. J.: Physiology in Health and Disease, Philadelphia, Lea & Febiger, 1939). We have therefore omitted it in our calculations.

accompanied by an average drop of 13 per cent in oxygen consumption, an average rise of 26 per cent in the arteriovenous oxygen difference and an average decrease of 30 per cent in cardiac output and of 35 per cent in cardiac work. The basal metabolic rate did not change appreciably. There was an average decrease of 10 beats per minute in the pulse rate and of 11 mm. in the systolic blood pressure. Short résumés of the 5 cases are presented.

REPORT OF FIVE CASES

CASE 1.—A. D., a man aged 26, was 70 inches (178 cm.) tall and in perfect health (fig. 1). His initial weight of 202 pounds (92 Kg.) was 30 per cent greater than his ideal weight. The blood pressure was 120 systolic and 75 diastolic; the basal pulse rate, 68 per minute, and the oxygen consumption, 254 cc. per minute. The cardiac output measured 4.8 liters per minute. After being on a 1,200 calory diet for eleven weeks, he lost 32 pounds (15 Kg.), equivalent to 16 per cent of his initial weight. During that time, the blood pressure dropped to 100 systolic and 60 diastolic, and the pulse rate, to 56 per minute. The oxygen consumption fell to 200 cc. per minute, a drop of 20 per cent, and the arteriovenous oxygen difference increased 32 per cent. Simultaneously, the cardiac output dropped to 2.75 liters per minute, and the cardiac work was decreased from 5.9 to 3.0 kilogram-meters per minute. An appreciable change in oxygen consumption and cardiac output did not occur until the fifth to the sixth week, after the patient had lost approximately 20 pounds (9 Kg.). After seventy-seven days the caloric intake was increased to 1,500; the weight was maintained, and the oxygen consumption, cardiac output and cardiac work increased slightly but remained below the initial levels.

CASE 2.—M. U., a 40 year old housewife, was 71 inches (180 cm.) tall and weighed 230 pounds (104 Kg.), that is, 27 per cent more than her ideal weight (fig. 2). The blood pressure was 115 systolic and 75 diastolic and the pulse rate, 70 per minute. The initial cardiac output measured 3.75 liters per minute, and the cardiac work, 5.1 kilogram-meters per minute. During a period of approximately seven months on a low calory diet the subject lost 35 pounds (16 Kg.), that is, 15 per cent of the initial weight. This loss was accompanied by a drop in oxygen consumption from 249 to 210 cc. per minute, representing a decrease of 16 per cent. The arteriovenous oxygen difference increased 23 per cent, and the cardiac output fell to 2.8 liters per minute, and the cardiac work, to 3.1 kilogram-meters per minute. The blood pressure dropped to 95 systolic and 68 diastolic, and the pulse rate, to 60 per minute. As in case 1, an appreciable effect was not noted until the eighth week, after the subject had lost 12 pounds (5 Kg.) in weight.

CASE 3.—E. B., a 15 year old boy, was 66 inches (167 cm.) tall and weighed 176 pounds (80 Kg.), which was 21 per cent above the ideal weight (fig. 3). On a 1,200 calory diet he lost only 6 pounds (3 Kg.) in three months. It was found that despite this slight loss of weight the arteriovenous oxygen difference rose 40 per cent, the cardiac output fell from 4.6 to 3.3 liters per minute and the cardiac work decreased from 5.1 to 4.1 kilogram-meters per minute. This apparent discrepancy was explained by the fact that the subject's height had increased 3 inches (7 cm.). Growth is normally accompanied by an increase in oxygen consumption, but the latter remained approximately the same in this growing boy while he was on a low calory diet. Therefore, there was actually

TABLE 1.—*Effects of Undernutrition on the Heart and the Circulation in Overweight Subjects*

Subject	Sex	Age, Yr.	Height, In.	Weight, Lb.		Pulse Rate per Min.	Blood Pressure, Mm. Hg	Vital Capacity, Cc.	Basal Metabolic Rate, %	Oxygen Consumption, Cc./Min.	Arterio-venous Oxygen Difference, Cc./L.	Cardiac Output, L./Min.	Cardiac Work, Kg.-M./Min.
				Actual	Ideal								
A. D.	♂	26	70	202	155	68	120/75	3,000	−15	254	53	4.8	5.9
				170		56	100/60	3,500	−15	200	70	2.75	3.1
M. U.	♀	40	71	230	180	70	115/75	2,600	−8	249	65	3.75	5.1
				195		60	95/68	2,900	−9	210	80	2.8	3.1
E. B.	♂	15	66	176	145	76	100/60	3,200	−8	262	57	4.6	5.1
			69	170		70	105/65	3,500	−8	265	80	3.3	4.1
M. H.	♀	18	67	172	146	70	110/70	2,800	−16	225	65	3.5	4.5
				152		60	105/70	3,100	−13	192	79	2.5	2.9
J. F.	♀	50	64	179	150	68	120/80	2,900	−12	220	60	3.1	4.3
				157		58	105/70	3,200	−10	184	78	2.3	2.9
						Summary of Changes							
Range				−3 to −16%		−6 to −12	+5 to −20	+9 to +17%	+3 to −1%	+1 to −20%	+13 to +40%	−26 to −43%	−20 to −49%
Average				−12%		−10	−11	+12%	+1%	−13%	+26%	−30%	−39%

a relative decrease in oxygen consumption, and the loss in weight of 6 pounds is significant. The pulse rate and the blood pressure did not show any definite change.

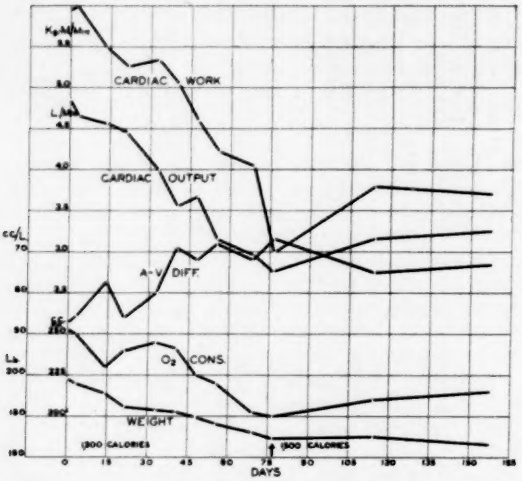

Fig. 1 (case 1).—A. D., a 26 year old man, 5 feet 10 inches (178 cm.) tall.

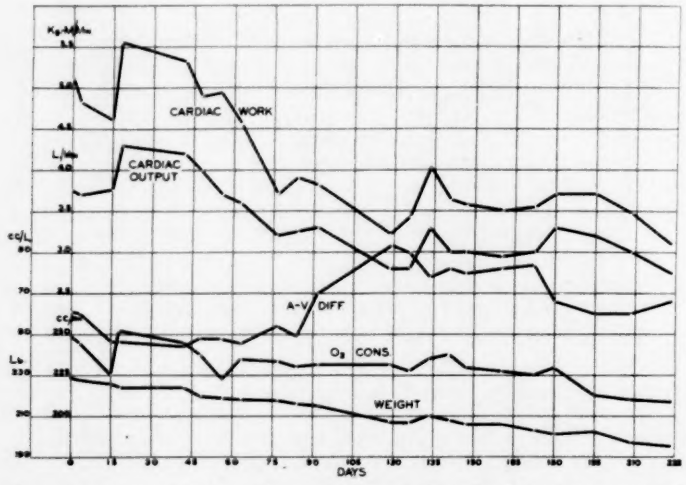

Fig. 2 (case 2).—M. U., a 40 year old woman, 5 feet 11 inches (180 cm.) tall.

CASE 4.—M. H., a woman aged 18, was 67 inches (170 cm.) tall and weighed 172 pounds (78 Kg.), 19 per cent above the ideal weight (fig. 4). After almost three months on a 1,200 calory diet she lost 20 pounds (9 Kg.). The oxygen

consumption fell from 225 to 192 cc. per minute, a drop of 15 per cent; the arteriovenous oxygen difference rose 22 per cent, and the cardiac output dropped from 3.5 to 2.5 liters per minute, a decrease of 28 per cent. The blood pressure

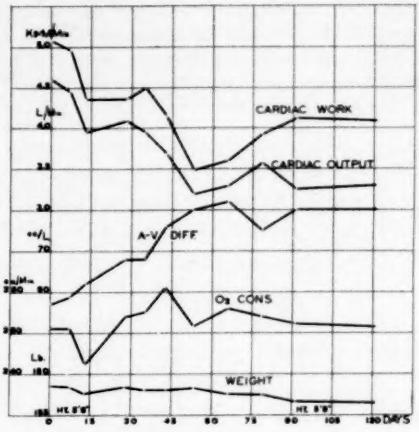

Fig. 3 (case 3).—E. B., a 15 year old boy, 5 feet 6 inches to 5 feet 9 inches (167 to 174 cm.) tall.

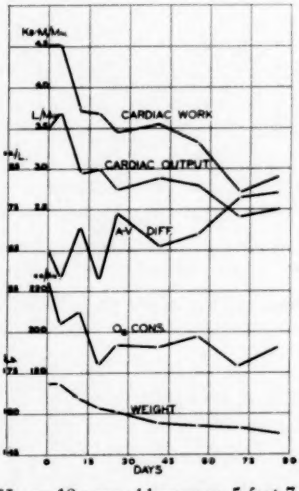

Fig. 4 (case 4).—M. H., an 18 year old woman, 5 feet 7 inches (170 cm.) tall.

did not change, but the pulse rate fell from 70 to 60 per minute. The cardiac work was diminished from 4.5 to 2.9 kilogram-meters per minute (36 per cent). Since the loss of weight was rapid during the first two weeks, distinct changes in circulatory dynamics were noted as early as the third week.

CASE 5.—J. F., a woman aged 50, was 64 inches (162 cm.) tall and weighed 179 pounds (81 Kg.), 20 per cent above the ideal weight (fig. 5). On a 1,200 calory diet she lost 22 pounds (10 Kg.) in approximately two months. During this period the oxygen consumption fell from 220 to 184 cc. per minute, a drop of 16 per cent, and the arteriovenous oxygen difference increased 13 per cent. The cardiac output dropped from 3.1 to 2.3 liters per minute and the cardiac work was reduced from 4.3 to 2.9 kilogram-meters per minute. The blood pressure dropped from 120 to 105 systolic and from 80 to 70 diastolic, and the pulse rate, from 68 to 58 per minute. The earliest effects were noted two weeks after institution of the low calory diet.

Comment.—Cardiac output was also measured in 3 cases in which the subjects did not lose any weight as a result of nonobservance of the diet or of endogenous factors. The cardiac output and other circulatory

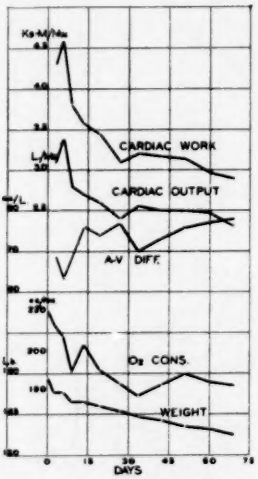

Fig. 5 (case 5).—J. F., a 50 year old woman, 5 feet 4 inches (157 cm.) tall.

factors did not change except for slight physiologic variations that occur from day to day.

COMMENT

It has been shown that undernutrition and reduction in weight in normal obese subjects slows the basal pulse rate and reduces the oxygen consumption, the cardiac output and the work of the heart. The reduction in cardiac output is determined chiefly by two factors: a fall in oxygen consumption, produced by the decrease in surface area occurring in undernutrition, and a rise in arteriovenous oxygen difference, the so-called coefficient of oxygen utilization. The increased arteriovenous oxygen difference is a manifestation of improved oxygen utilization and accounts for the fact that the decrease in cardiac output is proportionally

greater than that in oxygen consumption. The cardiac work is reduced, since it is proportional to cardiac output and peripheral resistance, as measured by mean arterial pressure. The reduction in the work of the heart was actually 33 to 49 per cent in 4 of the 5 cases reported. The pulse rate and the pulse pressure decreased with weight reduction. The drop in pulse rate, a vagal effect brought about by the lowered metabolic rate, increases the efficiency of the heart, since diastole is prolonged.

In previous studies in undernutrition by Benedict [1] and Master [2] and their associates a distinct lowering of the basal metabolic rate as well as of the oxygen consumption was observed. Only a minority of subjects in these two series were overweight. In our overweight subjects there was no definite effect on the basal metabolic rate despite the diminution in total body metabolism.

Another advantageous change noted in our subjects was an increase of 10 to 17 per cent in vital capacity. As stated previously, obesity is associated with elevation of the diaphragm, which limits the respiratory movements and places a great burden on the pulmonary circulation. Loss of weight is accompanied by a lowering of the diaphragm, facilitating expansion of the lungs and increasing vital capacity. The latter results in improved exercise tolerance and diminution of dyspnea on effort.

An important application of the circulatory effects of undernutrition lies in the treatment of patients with cardiac disease, particularly those who are overweight, in whom dietary restriction causes an increase in cardiac reserve, combats the tendency to heart failure and prevents attacks of angina pectoris on effort by decreasing the basal work of the heart. Effort results in increased muscular action, which in turn augments the requirements for oxygen, cardiac output and coronary circulation. Since there is a disproportion between oxygen requirement and supply in the presence of coronary artery disease, angina pectoris due to coronary insufficiency occurs. Under such circumstances reduction in weight acts beneficially by lowering the basal cardiac output and raising the threshold for anginal attacks. For example, if the basal cardiac work is 5.9 kilogram-meters per minute (case 1), the limit of coronary supply is reached quickly during effort. After reduction in weight the basal cardiac work is lowered, in this case to 3.0 kilogram-meters per minute, allowing for greater increase in coronary circulation and thus raising the threshold for an anginal attack by 2.9 kilogram-meters per minute. This is the chief benefit of undernutrition to patients with coronary artery disease. Restriction of the diet of patients with such disease, particularly if they are overweight, is of the utmost importance in the prevention of attacks of angina pectoris.

SUMMARY

The effect of reduction in weight on the oxygen consumption, pulse rate, blood pressure, cardiac output and cardiac work was studied in 5 normal overweight subjects who were placed on a 1,200 calory diet. The modified Grollman acetylene method and the Wetzler-Boeger physical method were used to determine the cardiac output. Loss of weight was accompanied by an average drop of 16 per cent in oxygen consumption, an average increase of 24 per cent in the arteriovenous oxygen difference and an average drop of 30 per cent in the cardiac output. These changes were accompanied by slowing of the pulse rate and slight lowering of the blood pressure. Since cardiac work is a function of cardiac output and mean arterial pressure, it was calculated that the low caloric intake and the reduction in weight resulted in a distinct diminution in the work of the heart (average, 35 per cent). This is of great benefit to overweight persons, in whom the cardiac work is increased, and is of particular importance in the treatment of patients with heart disease, whose cardiac reserve is diminished and who are barely able to compensate for any additional strain.

PERSISTENCE AND RECURRENCE OF TOXIC GOITER FOLLOWING SUBTOTAL THYROIDECTOMY

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While subtotal thyroidectomy is a successful procedure in most patients with toxic goiter, it is followed in some instances by the persistence or recurrence of signs and symptoms of the disease. In a previous study one of us (W. O. T.) and associates [1] reported observations on patients with postoperative thyrotoxicosis seen at the Massachusetts General Hospital, Boston. The present study was undertaken to compare the disease in an area in which simple goiter is prevalent (Chicago) with that in an area in which simple goiter is rare (Boston) and to secure further information concerning the cause, duration and types of postoperative thyrotoxicosis. It represents an analysis of data obtained on 294 patients with toxic goiter on whom subtotal thyroidectomy was performed and who were followed before and after operation in the endocrine clinic of the Presbyterian Hospital.

FOLLOW-UP STUDY

This study covers the ten year period 1930 to 1939. During this time 548 patients who had been operated on for toxic goiter reported to the clinic. Of this number, 208 were unsuitable for this study. Some of them had had only one hemithyroidectomy and had then disappeared from observation. Others had been operated on in another clinic, and their course of illness before the operation, the diagnosis and the extent of the thyroidectomy were not well known. We also excluded 46 patients who had been followed up for less than three months after operation. This leaves 294 patients who were known to have had a subtotal thyroidectomy and who were followed up more than three months after operation.

An attempt was made to see every patient at two to three month intervals for the first year after operation. After the first year, as many patients as possible

From the endocrine clinic, Presbyterian Hospital, and the Department of Medicine, University of Illinois College of Medicine.

1. Thompson, W. O.; Morris, A. E., and Thompson, P. K.: Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter, Arch. Int. Med. **46:** 946-978 (Dec.) 1930.

TABLE 1.—*Course of the Basal Metabolic Rate in the Thirty-Nine Patients Who Were Thyrotoxic After Subtotal Thyroidectomy* *

Patient †		Age at Time of Operation,	Basal Metabolic Rate			
No.	Sex	Yr.	At Time of Admission to Hospital	Just Before Operation	At Time of Discharge from Hospital	Summary of Basal Metabolic Rates After Discharge
1	♀	34	+57	+22 ‡	+ 2 ‡ (12)	+31 (70); +18 (170); +15 (177); +9 (213), pregnant; +28 (229); +22 (243); +25 (264); +17 (301)‡; +20 (334)‡; +28 (517); +6 (608)‡
2	♂	57	+75	+32 ‡	+36 ‡ (7)	+26 (50)‡; +38 (79)‡; +37 (135); +10 (193); +12 (338); +48 (429); +27 (531); +6 (557); +3 (673); —4 (703)‡; —5 (837)‡
3	♀	35	+44	+28 ‡	+ 0 ‡ (33)	+10 (37)‡; +13 (77); +25 (161); +25 (194); +17 (268)‡; +20 (310)‡; +19 (351)
4	♀	35	+50	+50 ‡	.....	+83 (2,078); +40 (2,136)‡; +25 (2,193)‡; +35 (2,201); +51 (2,299)‡
5	♀	16	+ 7 ‡	— 2 ‡	+ 4 ‡ (7)	+4 (47); +3 (69); —1 (111); +3 (174); +4 (205); +11 (494)‡; +2 (504); —4 (809); —7 (1,162); +1 (1,491); +1 (1,498); +25 (1,786); +32 (1,792); +19 (1,813)‡; +7 (1,872)‡; +17 (1,906)‡; +19 (1,940)‡; +12 (1,982)‡; +5 (2,042); +5 (2,129)
6	♂	42	+54 ‡	+48 ‡	+11 ‡ (11)	+33 (36); +47 (43); +24 (99)‡; +7 (130)‡; +7 (165)‡; +15 (210);+20 (247); +37 (319); —7 (342)‡; +4 (345)‡; +35 (503); +35 (505); +19 (573)‡
7	♀	38	+74	+12 ‡	+12 ‡ (7)	+16 (25); +0 (104); —19 (165); —14 (191)‡; +4 (325); —10 (355)‡; +22 (1,272); +23 (1,295); +29 (2,879); +30 (3,347); +24 (3,351)‡
8	♀	18	+64 ‡	+25 ‡	— 1 ‡ (13)	0 (44)‡; +29 (77); +23 (135); +21 (167); +10 (239); +10 (351)
9	♀	35	+40 ‡	+40 ‡	.....	+26 (33); +66 (91); +31 (114)‡; +71 (161)
10	♀	28	+48	+32 ‡	+30 ‡ (9)	See chart 2
11	♀	43	+48	+31 ‡	+27 ‡ (12) +14 ‡ (15)	See chart 5
12	♀	44	+38 ‡	+38 ‡	+ 9 ‡ (12)	See chart 6
13	♀	49	+17	— 2 ‡	.....	+22 (24); +23 (61); +15 (306); +17 (543); +3 (925); +4 (1,827)
14	♀	38	+36 ‡	+36 ‡	.....	+27 (587); +13 (651); +27 (709); +19 (785); +22 (942); +22 (1,022); +19 (1,179); +25 (1,272); admission to hospital; —3 (1,283)‡; —3 (1,254)‡; —7 (1,287)‡; subtotal thyroidectomy; —4 (1,321); +3 (1,361); —6 (1,481); +10 (2,435)
15	♀	45	+ 9	+13 ‡	.....	See chart 3
16	♂	33	+48 ‡	+33 ‡	+30 ‡ (10)	0 (20)‡; +7 (55); +16 (86); +33 (223); +21 (283); +24 (574)
17	♀	20	+34	— 3 ‡	+ 9 ‡ (7)	+19 (104); +15 (199)‡; +12 (297)‡; +17 (426)‡; +13 (476)‡; +31 (536); +34 (578); +38 (615)
18	♀	48	+33 ‡	+20 ‡	.....	+17 (45); +13 (209); +19 (231); +14 (294)‡; +15 (383); +21 (420); +30 (521); +35 (577)‡; +35 (662); +27 (812)

19	♀	18	+52 ‡	+32 ‡	+20 ‡ (7)	+22 (23); −2 (84)‡; +2 (126)‡; +15 (147)‡; +15 (175)‡; +18 (280); +23 (323); +13 (434)‡; +28 (539); +9 (609)‡; −1 (859)‡; −1 (984)‡; −3 (1,068)‡; −2 (1,195)‡; +4 (1,726); +1 (1,859); +2 (2,346)
20	♀	30	+49	+31 ‡	+ 8 ‡ (7)	+19 (39); +18 (90); +17 (222)‡
21	♀	45	+55 ‡	+37 ‡	.....	+42 (46); +34 (67); +39 (100); +14 (128)‡; +29 (195); +12 (231); +5 (280)‡; +18 (368); +9 (459); +6 (554); +2 (948); 0 (1,300)
22	♀	44	+55	+35 ‡	+21 ‡ (4)	+21 (38); +31 (53); +13 (77); +6 (131)‡; −1 (204)‡; +22 (279); +27 (357); −7 (434)‡; +3 (524)‡; −7 (713)‡; −4 (776)‡; +2 (907)‡; +6 (952)§
23	♂	50	+18	+10 ‡	.....	Admission to hospital: +39 (181); +35 (182); +43 (183)‡; +41 (186); +40 (188); +26 (198)‡; +29 (211); subtotal thyroidectomy; +4 (220); −7 (318); +6 (636); +4 (951); −11 (1,014)
24	♀	44	+32	+18 ‡	.....	+47 (157); +17 (192); +18 (284); +48 (2,100); +36 (2,104); −4 (2,146)‡; −7 (2,174)‡; −15 (2,209); −3 (2,230)
25	♀	50	+63	+31 ‡	+12 ‡ (7)	See chart 4
26	♀	12	+43	+25 ‡	− 2 ‡ (6)	See chart 1
27	♀	40	+74 ‡	+79 ‡	+20 ‡ (10)	+37 (150)
28	♀	17	+52	+17 ‡	+ 2 ‡ (7)	Admission to hospital; +35 (678); +31 (679); +30 (680); +31 (682); +15 (680)‡; +7 (712)‡; subtotal thyroidectomy; +6 (725)‡; +17 (822); +6 (832)‡; 0 (850); +2 (1,164); −5 (1,899); −4 (2,324)
29	♀	47	+62	+59 ‡	+47 ‡ (8)	+37 (45); +28 (76)‡; +23 (131); +68 (195)‡
30	♀	20	+47	+28 ‡	+ 6 (10)	+29 (95); +27 (144); −12 (1,209)
31	♂	35	+54	+35 ‡	+14 ‡ (8)	+17 (89); +22 (138); +6 (187)‡; +31 (257); +35 (517); +10 (741); +14 (797)
32	♀	29	+52	+18 ‡	+23 ‡ (8)	+30 (76); +21 (97)
33	♀	58	+41 ‡	+47 ‡	+19 ‡ (14)	+35 (107); +18 (158); +11 (219); +11 (882)
34	♂	56	+28	+ 7 ‡	+ 8 ‡ (8)	+24 (35)‡; +27 (104)‡; +7 (134)‡; +25 (181)‡; +35 (191)‡; +21 (333)‡; +24 (454)‡; +32 (762)‡
35	♀	52	+69	+14 ‡	+ 1 ‡ (7)	+24 (47); +15 (148); −8 (165)‡; −8 (313)‡; +20 (794)
36	♀	57	+76	+57 ‡	+20 (9)	−3 (16); +11 (72); +17 (88); +28 (140); +21 (201)
37	♀	21	+44	+28 ‡	+13 ‡ (7)	+22 (130); +32 (172); +21 (208); +34 (268); +32 (274); +28 (278); +15 (281); +19 (292); +15 (313); +13 (327); +20 (331); +16 (341); +4 (347); 0 (389); +3 (442); +4 (738); +8 (1,398)
38	♀	40	+56 ‡	+24 ‡	+19 ‡ (7)	+36 (60); +1 (134)‡; +25 (155); +6 (214)‡; −10 (314)‡; −2 (540)‡; −10 (810); −19 (908); −7 (1,170); −15 (1,825)
39	♀	27	+68	+34 ‡	+29 ‡ (12)	+20 (72); +12 (128); +7 (185)‡; −9 (240)‡, pregnant; +20 (335); +26 (369)‡; +32 (408)‡; second thyroidectomy

* This table gives only an outline of the variation in the basal metabolic rate, expressed as the percentage of the normal rate. In most instances, many more determinations were done. The figures in parentheses denote the number of days after operation.

† In patients 10 and 13 the diagnosis was toxic adenoma and in the remainder exophthalmic goiter.

‡ Basal metabolic rate determined during medication with iodine.

§ Basal metabolic rate determined during medication with thyroid.

were observed at intervals of six months to one year. Patients who were not completely well because of persistence or recurrence of the disease, vocal cord paralysis, parathyroid tetany, postoperative hypothyroidism or some other complication were observed at more frequent intervals. The patients were observed for the following lengths of time:

Duration of Follow-Up After Operation	No. of Patients
3 to 11 mo.	99
1 to 3 yr.	125
4 to 7 yr.	53
Over 7 yr.	17

Each time a patient returned to the clinic for examination a determination of the basal metabolic rate was made with the Sanborn-Benedict apparatus and the Aub-Du Bois standards.

TYPE OF OPERATION

The subtotal thyroidectomy was usually done in one stage, but in 27 patients (in 8 of whom postoperative thyrotoxicosis developed and in 19 of whom there was no later evidence of postoperative thyrotoxicosis) two hemithyroidectomies were performed several months apart. In 7 patients (6 without and 1 with postoperative thyrotoxicosis) preliminary polar ligations were done to test the patients' ability to withstand surgical manipulation. About 80 per cent of the operations were done by eight surgeons who do a considerable amount of thyroid surgery; the other 20 per cent were distributed among twenty-one surgeons, some of whom do only occasional thyroidectomies. There was, therefore, no standardization of technic, the amount of tissue left in at operation varying with the different surgeons. The amount of thyroid tissue removed, according to the notes made at operation, usually varied from two thirds to nine tenths of the gland.

INCIDENCE OF THYROTOXICOSIS FOLLOWING SUBTOTAL THYROIDECTOMY

There were 39 instances of postoperative thyrotoxicosis among the 294 patients (13 per cent). Of these, 37 occurred among 212 patients with exophthalmic goiter (17.5 per cent) and only 2 among 82 patients with toxic adenoma (2.4 per cent). The remaining patients appeared to be cured; that is, they showed no definite signs or symptoms of thyrotoxicosis after operation and their basal metabolic rate was normal or less than normal. The data on the 39 patients thyrotoxic after operation are summarized in table 1.

In evaluating the presence of postoperative thyrotoxicosis, we considered several factors: the presence of clinical signs and symptoms, such as tachycardia; undue nervousness; ease of fatigue; excessive sweating; loss of weight, and persistent elevation of the basal metabolic rate above the normal. (In general, plus or minus 15 per cent was taken as the normal range.) Many patients who had a slight elevation

of the basal metabolic rate at some time following operation were not included in the group of those who had postoperative thyrotoxicosis because other signs and symptoms of the disease were wanting. No patient was considered to be thyrotoxic unless the basal metabolic rate was consistently + 15 per cent or higher without iodine therapy.

SEVERITY OF POSTOPERATIVE THYROTOXICOSIS

Although 39 patients were thyrotoxic at some time after operation, only 9 failed to show some symptomatic improvement, and in only 3 (patients 4, 9 and 15) was the thyrotoxicosis worse after subtotal thyroidectomy than before. On the basis of basal metabolism determin-

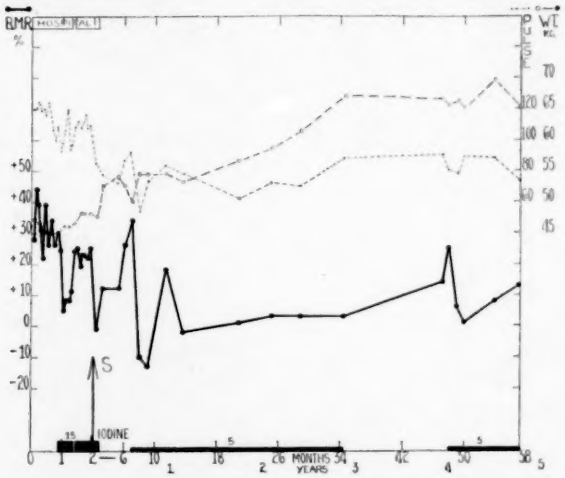

Chart 1 (patient 26).—Typical mild persistence of thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter. Note that the presence of thyrotoxicosis was masked by the administration of iodine just after operation. This chart shows that iodine may hold the basal metabolic rate within normal limits for many months. The following symbols are used in some or all of the charts: *H*, hospitalization; an arrow and *S*, subtotal thyroidectomy; black areas, periods of treatment with compound solution of iodine U. S. P., with the daily dose in minims indicated above each area, and cross hatched areas, periods of treatment with thyroid with the daily dose in grains indicated above each area.

ations in the 39 patients thyrotoxic after operation, the disease was mild (+ 15 per cent to + 29 per cent) in 54 per cent, moderately severe (+ 30 per cent to + 59 per cent) in 38 per cent and severe (+ 60 per cent or higher) in 8 per cent, whereas in the same patients before operation it was mild in 10 per cent, moderately severe in 67 per cent and severe in 23 per cent.

PERSISTENCE AND RECURRENCE OF THYROTOXICOSIS

A distinction was made between patients in whom the disease disappeared after operation and recurred at a later date and those in whom it persisted. The thyrotoxicosis was considered persistent when there was evidence that the disease had not disappeared temporarily after the operation except under the influence of iodine. The thyrotoxicosis was considered recurrent only when there was evidence to show that there was a period after operation when without medication it was not present. On this basis it persisted in 30 patients and recurred in 5, while in 4 instances the data were insufficient to determine the type.

TABLE 2.—*Comparison of Basal Metabolic Rates During Administration of Iodine Shortly After Thyroidectomy* in Patients Who Were Thyrotoxic and in Those Who Were Not*

(Exophthalmic Goiter)

Basal Metabolic Rate, Percentage of the Normal Rate	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
+30 or over	3	10.3	7	4.8
+25 to +29	1	3.5	5	3.5
+20 to +24	5	17.2	11	7.6
+15 to +19	2	6.9	16	11.0
+10 to +14	6	20.7	22	15.2
+ 5 to + 9	5	17.2	27	18.6
0 to +14	5	17.2	21	14.5
− 5 to −1	2	6.9	19	13.1
−10 to −6	0	0.0	12	8.3
Below −11	0	0.0	5	3.5

* Six to twelve days afterward in most instances.

ONSET OF PERSISTENT THYROTOXICOSIS

Thompson and associates [1] have previously shown that when toxic goiter disappears after subtotal thyroidectomy the basal metabolic rate tends to fall to within normal limits ten to fourteen days after operation during the administration of iodine and that when the operation fails to cure the disease the rate tends to remain above + 15 per cent in about 40 per cent of cases. A similar percentage of patients show the same amount of elevation in the present series (table 2), but there is less difference between those with postoperative thyrotoxicosis and those without postoperative thyrotoxicosis, probably because the basal metabolic rates were determined sooner after operation in this series than in that of Thompson and associates. In those patients whose metabolic rate was normal during the administration of iodine at the time of discharge from the hospital, the persistence was usually first noticed shortly after iodine was discontinued.

COURSE OF PERSISTENT THYROTOXICOSIS

During the time of observation the disease disappeared without any treatment except iodine in 11 (37 per cent) of the 30 patients in whom thyrotoxicosis persisted; that is, these patients ceased to require treatment to maintain their metabolism within normal limits. These remissions took place from about four months to about three years after operation. In the remaining 19 patients the disease persisted for the duration of the follow-up study or until a second thyroidectomy was done. Four of them showed a tendency to improve gradually. In other words, the level to which iodine depressed the metabolism or the level to which the metabolism rose after omission of iodine gradually decreased.

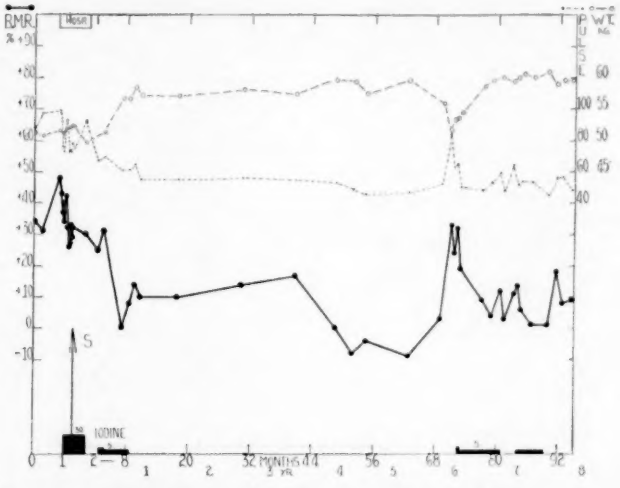

Chart 2 (patient 10).—Recurrence of toxic adenoma about six years after subtotal thyroidectomy and control of thyrotoxicosis by iodine until it finally disappeared. The recurrence was associated with marked regeneration of thyroid tissue. For explanation of the symbols see chart 1.

The remaining 15 patients showed no tendency to improve under iodine therapy, and 4 of them gradually became worse, as judged by the level of metabolism.

ONSET AND COURSE OF RECURRENT THYROTOXICOSIS

As previously stated, a true recurrence was noted in 5 patients. Two of them were well after operation until the onset of the recurrence, between one and three years after operation (patient 7) and between four and five years after operation (patient 5), respectively. The

other 3 patients (15, chart 3; 25, chart 4, and 10, chart 2) had some residual symptoms of thyrotoxicosis, which persisted from three and a half to eight months after operation, after which interval a remission took place, and they were then well until the onset of the recurrence, about two, four and a half and six years after thyroidectomy, respectively.

Of the five recurrences of thyrotoxicosis, one lasted twenty-two months, until a second thyroidectomy was done; one lasted somewhere between five and fourteen months and disappeared spontaneously, and three lasted for the duration of the follow-up study (eight months, two years and three and one-half years, respectively).

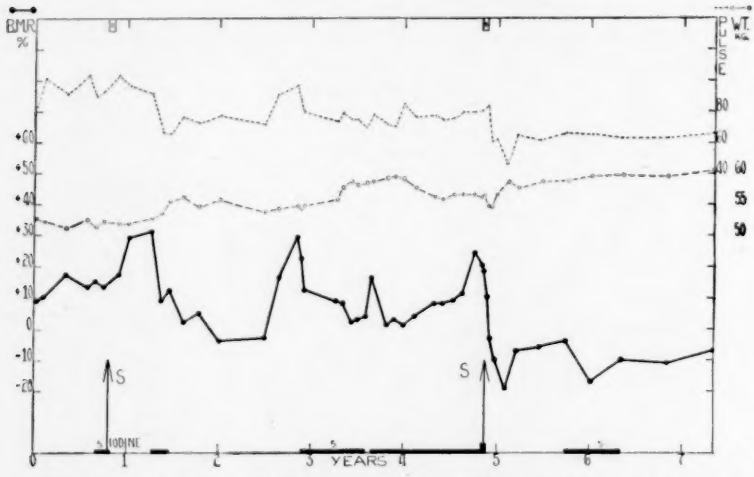

Chart 3 (patient 15).—Spontaneous remission of exophthalmic goiter between six and ten months after subtotal thyroidectomy and a later recurrence of the disease between twenty and twenty-two months after operation. The recurrence was accompanied by marked regeneration of thyroid tissue and finally required a second thyroidectomy. For explanation of the symbols see chart 1.

CAUSES OF POSTOPERATIVE THYROTOXICOSIS

Miscellaneous Factors.—In tables 3 to 7 data on age incidence, sex distribution, duration of symptoms at the time of operation, basal metabolic rate at the time of admission to the hospital and size of the thyroid gland before operation in the patients with exophthalmic goiter who were thyrotoxic after operation are compared with similar data on those who were not. The figures for the two groups are about the same, the only difference being that the average duration of symptoms was somewhat less for those with postoperative thyrotoxicosis. An analysis of these

factors in 190 patients with exophthalmic goiter studied in Boston also failed to show any clearcut difference between the two groups.

In our experience postoperative thyrotoxicosis occurs infrequently among patients with so-called toxic adenoma, there being only 2 instances

TABLE 3.—*Age of Patients with Exophthalmic Goiter at the Time of Operation*

Age, Yr.	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Under 20	5	13.5	10	5.7
20 to 29	5	13.5	27	15.4
30 to 39	9	24.3	57	32.6
40 to 49	11	29.7	54	30.9
50 to 59	7	18.9	20	11.4
60 or over	0	0.0	7	4.0
	37		175	
Average age	37.9		38	
Highest age	57		74	
Lowest age	12		13	

TABLE 4.—*Sex of Patients with Exophthalmic Goiter*

	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Male	6	16.2	35	20.0
Female	31	83.8	140	80.0
	37		175	

TABLE 5.—*Duration of Symptoms at the Time of Operation in Patients with Exophthalmic Goiter*

Duration	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Less than 6 months	11	29.7	58	33.1
6 to 11 months	10	27.0	41	23.4
1 to 2 years	6	16.2	25	14.3
Over 2 years	9	24.3	40	22.9
Unknown	1	2.7	11	6.3
	37		175	
Shortest duration	1 month		3 weeks	
Longest duration	5 years		17.5 years	
Average duration	18.6 months		22.7 months	

among 82 patients in the present series. The question of the accuracy of the diagnosis in these 2 instances naturally arises. Plummer did not find any instances of postoperative thyrotoxicosis in a large series of patients with toxic adenoma.[2]

2. Plummer, H. S.: The Function of the Thyroid Gland Containing Adenomatous Tissue, Tr. A. Am. Physicians **43**:159, 1928.

Possible Precipitating Factors.—Pemberton [3] expressed the belief that infections, overwork, worry, fright, shock, pregnancy and operations are important factors in recurrences. Berlin and Gargill [4] concluded from a study of 11 recurrences of the disease that inadequate thyroidectomy played less of a role than other factors, such as psychic trauma, infections, pregnancy, tuberculosis, the menopause and the personality of the patient. In only a few instances could we find such factors operative

TABLE 6.—*Basal Metabolic Rate at the Time of Admission to the Hospital in Patients with Exophthalmic Goiter*

Basal Metabolic Rate, Percentage of Normal *	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Below +40	9	24.3	70	40.0
+40 to +49	9	24.3	28	16.0
+50 to +59	10	27.0	29	16.6
+60 and over	9	24.3	48	27.4
	37		175	
Highest rate	+76		+113	
Lowest rate	+ 7		— 2	
Average rate	+48.5		+ 46.1	

* In a few cases the basal metabolic rate was determined during the administration of iodine.

TABLE 7.—*Size of the Thyroid Before Operation in Patients with Exophthalmic Goiter*

Size of Thyroid	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Not enlarged	1	2.7	8	4.6
Slightly enlarged	11	29.7	48	27.4
Moderately enlarged	20	54.0	101	57.7
Markedly enlarged	5	13.5	18	10.3
	37		175	

in our patients. Pleurisy with effusion developed in 1 patient (10, chart 2) after an infection of the upper respiratory tract. Coincident with the termination of this infection, elevation of the basal metabolic rate and return of symptoms of fatigue, nervousness and tachycardia

3. Pemberton, J. deJ.: Recurring Exophthalmic Goiter: Its Relation to the Amount of Tissue Preserved in Operation on the Thyroid Gland, J. A. M. A. **94**:1483-1489 (May 10) 1930.

4. Berlin, D. D., and Gargill, S. L.: Factors Influencing Persistent and Recurrent Hyperthyroidism, New England J. Med. **222**:254-259 (Feb. 15) 1940.

were noticed. In the other 4 patients with recurrence of the disease there was no associated disturbance in the nature of infection, the menopause or unusually upsetting emotional experiences. In 1 patient (19) who had a severe cold accompanied by a sore throat about twice a year, we observed a remission of the disease after it had persisted for two years after thyroidectomy. For the ensuing five years there was no elevation of the basal metabolic rate, although the colds continued unabated. In another patient (2) persistent thyrotoxicosis increased in severity on two occasions during a severe cold, but in each instance the metabolic level promptly reestablished itself when the cold subsided. In only 3 patients was postoperative thyrotoxicosis complicated by preg-

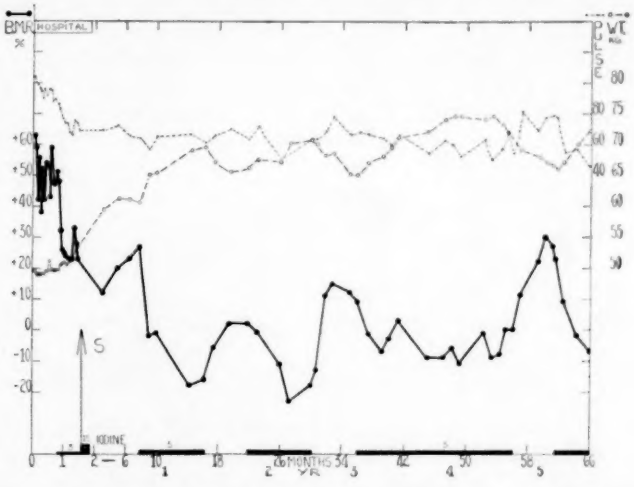

Chart 4 (patient 25).—Persistence and recurrence of exophthalmic goiter. The disease persisted for at least six months after subtotal thyroidectomy. The patient was then well for nearly five years, but during this time the levels of the basal metabolism with and without iodine gradually rose. A recurrence took place about five years after operation. For explanation of the symbols see chart 1.

nancy. Two of them (patients 1 and 39) had slightly lower metabolic rates during pregnancy, but after delivery the rates reverted to the prepartum level. A third patient (28) became more thyrotoxic during pregnancy.

Our data suggest that infections, unusually upsetting emotional experiences, pregnancy and the menopausal syndrome are not important factors in the onset of persistent and recurrent thyrotoxicosis. If they play any role at all, it is probably merely as precipitating factors.

AMOUNT OF THYROID TISSUE PALPABLE AFTER OPERATION

Cattell and Morgan [5] reported that palpation of the thyroid gland after operation is frequently unreliable because the scar tissue resulting from the previous thyroidectomy makes it difficult to outline the lateral lobes. In our experience, palpation is difficult only for a few weeks after operation, until induration disappears. In many patients, thyroid tissue can then easily be palpated and can often be observed to regenerate or regress in amount. In table 8 is expressed the maximum amount of thyroid tissue palpable after operation. "Questionable" means that the thyroid tissue was sufficiently difficult to palpate to render its presence open to question. "Definitely" signifies that the tissue could be felt, and

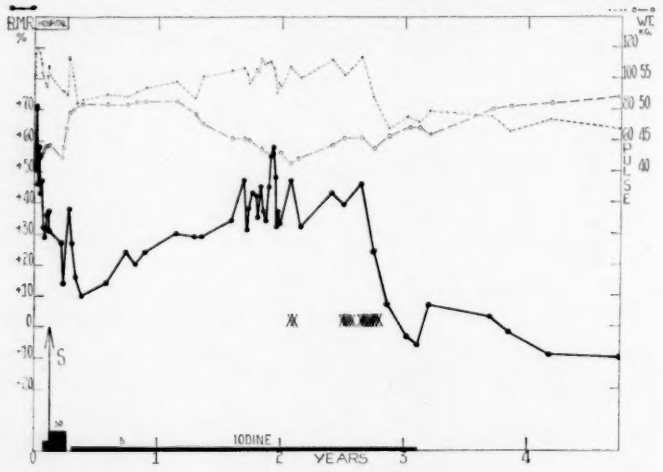

Chart 5 (patient 11).—Persistence of thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter, with a gradual rise in the metabolic rate during prolonged administration of iodine. A remission took place about three years after operation following roentgen ray therapy. *X* denotes roentgen ray treatment over the thyroid. For explanation of the other symbols see chart 1.

the mass varied in amount up to 1.5 cm. in diameter. "Considerable" is used to include all masses of thyroid tissue larger than 1.5 cm. in diameter. It is of interest that of 286 patients on whom frequent observations were made, 108 (38 per cent) had sufficient thyroid tissue present to be palpable at some time after operation. The incidence of palpable thyroid tissue and of regeneration of thyroid tissue was greater in

5. Cattell, R. B., and Morgan, E. S.: Recurrent Hyperthyroidism, Surg., Gynec. & Obst. **68**:347-351 (Feb.) 1939.

patients who were thyrotoxic after operation than in those who were not. Thus it may be seen in table 8 that 32 patients (89 per cent) with postoperative thyrotoxicosis had palpable thyroid tissue at some time following operation, as compared with 76 (30 per cent) of those without thyrotoxicosis. Only 4 patients in the former group had no palpable tissue, and in each of these patients thyrotoxicosis was mild.

Similarly, regeneration of thyroid tissue was noted much more frequently among patients with postoperative thyrotoxicosis. Of 31 patients on whom frequent observations were made, 23 (74 per cent) showed some regeneration, while of 230 patients without postoperative thyrotoxicosis, only 34 (15 per cent) showed regeneration of thyroid tissue. That thyrotoxicosis, even of a severe nature, may occur in the presence of a small amount of thyroid tissue or in the absence of any palpable thyroid tissue has been pointed out by Haines and Pemberton,[6] Moor-

TABLE 8.—*Maximum Amount of Thyroid Tissue Palpable* After Operation in Patients with Toxic Adenoma and with Exophthalmic Goiter*

	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Palpation attempted	36		250	
Palpable tissue absent	4	11.1	174	69.6
Palpable tissue present	32	88.9	76	30.4
Questionable amount of tissue present	2	6.2	17	22.4
Definite amount of tissue present	15	46.9	38	50.0
Considerable amount of tissue present	15	46.9	21	27.6

* For definition of the terms used to describe the amount of tissue palpable see the section in the text headed "Amount of Thyroid Tissue Palpable after Operation."

head[7] and Phemister and Delaney.[8] However, such occurrences are the exception rather than the rule. In general, the presence of palpable amounts of thyroid tissue after operation is fairly strong presumptive evidence of the presence of thyrotoxicosis.

RELATION OF POSTOPERATIVE THYROTOXICOSIS TO THE AMOUNT OF THYROID TISSUE LEFT IN AT OPERATION

Bowers[9] expressed the opinion that the amount of thyroid tissue left by the surgeon determines the incidence of persistent and of recurrent thyrotoxicosis. His study of 302 patients showed that the surgeon with

6. Haines, S. F., and Pemberton, J. deJ.: Control of Hyperthyroidism Following Partial Thyroidectomy, Arch. Int. Med. **57**:1104-1114 (June) 1936.

7. Moorhead, T. G.: Athyroid Thyrotoxicosis, Irish J. M. Sc., February 1940, pp. 80-81.

8. Phemister, D. B., and Delaney, P. A.: Thyrotoxicosis Continuing After Extreme Operative, Iodine, and Roentgen Therapy, J. A. M. A. **100**:568 (Feb. 25) 1933.

9. Bowers, R. F.: Recurrent Toxic Goiter, West. J. Surg. **47**:536-542 (Sept.) 1939.

the lowest percentage of recurrences had the highest percentage of postoperative myxedema. In the series of 190 patients with exophthalmic goiter followed-up in Boston [1] the incidence of postoperative thyrotoxicosis was 14.4 per cent for three surgeons doing a large amount of thyroid surgery and 36.3 per cent for ten other surgeons who did relatively few thyroidectomies. Table 9 shows the incidence of postoperative thyrotoxicosis according to surgeons for the present study. It can be seen that the incidence among eight surgeons doing a large amount of thyroid surgery was 14.5 per cent, whereas for the surgeons doing thyroidectomies occasionally it was 28.3 per cent. We know from observation that surgeon B, who has the lowest incidence of post-

TABLE 9.—*Incidence of Postoperative Thyrotoxicosis According to Surgeons Performing the Thyroidectomies*

Surgeon	Number of Patients Operated On	Patients Thyrotoxic After Operation	
		Number	Percentage
A	43	7	16.3
B	30	1	3.3
C	21	4	19.0
D	19	4	21.1
E	19	3	15.8
F	13	2	15.4
G	9	1	11.1
H	8	2	25.0
21 other surgeons	46	13	28.3
Unknown	1	0	0.0
Total	212	37	
Surgeons doing the most thyroid surgery	106	24	14.5
21 surgeons doing only occasional thyroidectomies	46	13	28.3

	Number	Percentage
Patients with permanent paralysis of one vocal cord	28	9.5
Patients with permanent parathyroid tetany	11	3.7

operative thyrotoxicosis, does a rather extensive subtotal thyroidectomy. It was also true in the Boston series that the more experienced surgeons performed more extensive thyroidectomies and had the smallest incidence of postoperative thyrotoxicosis. Many other observers [10] have

10. Else, J. E.: Prevention of Recurrent Goiter, S. Clin. North America **8**: 1375-1394 (Dec.) 1928. Gilman, P. K., and Kay, W. E.: Certain Advantages of Total Thyroidectomy in Selected Cases of Thyrotoxicosis of the Exophthalmic Type, Am. J. M. Sc. **175**:350-360 (March) 1928. Lahey, F. H.: Review of Another Year's Work with Thyroid Disease, Boston M. & S. J. **190**:153-156 (Jan.) 1924. Elliott, C. A.: The Control of Hyperthyroidism by Thyroidectomy: Results in One Hundred Cases, J. A. M. A. **89**:519-522 (Aug. 13) 1927. Smith, L. W.; Clute, H. M., and Streider, J. W.: The Results in One Hundred Consecutive Cases of Hyperthyroidism Operated Upon, Surg., Gynec. & Obst. **46**:325-331 (March) 1928. Waits, C. E.: Preoperative and Postoperative Studies in Goiter, J. M. A. Georgia **11**:355 (Sept.) 1922. Clute, H. M.: Hyperthyroidism Persisting After Thyroidectomy: The Necessity for Postoperative Examinations in Toxic Goiters, S. Clin. North America **6**:691-694 (June) 1926. Cattell and Morgan.[5]

stated that one of the chief causes of thyrotoxicosis following subtotal thyroidectomy is the removal of too little thyroid tissue. This is supported in our series by the fact that there was no outstanding difference before operation between the patients who were thyrotoxic after operation and those who were not and perhaps to some extent by the greater percentage of patients who had palpable thyroid tissue after operation among those with thyrotoxicosis than among those without thyrotoxicosis. In 1 patient (9) in whom there was a considerable amount of thyroid tissue palpable after operation the surgeon was forced to terminate the operation because of hemorrhage after a little more than a third of the gland had been removed. Within three months after operation the thyrotoxicosis was more severe than before operation. In cases of this kind it is quite obvious that the removal of more tissue would produce a better result.

Inadequate removal of thyroid tissue will not explain all the cases of persistence however. It seems to us of more than passing interest that the incidence of persistence of the disease was about the same for the more experienced surgeons in the Boston series as for those in the Chicago series, particularly since these two groups of patients were studied at different times and in entirely different parts of the country, one in which simple goiter is rare and one in which it is prevalent. We have seen patients in whom the disease persisted with rapid and extensive regeneration of thyroid tissue in spite of the removal of all but a small remnant of the thyroid gland. Under such circumstances the cause of the disease must still be active and perhaps is driving the gland to increased activity.

Recurrence of the disease presents an interesting problem. The patients who showed this phenomenon were free from the disease for a period of six months to five years after thyroidectomy, indicating that the thyroidectomy had been adequate. In every case there was regeneration of thyroid tissue at the time of recurrence. Similarly, in all but 8 patients with persistence of the disease regeneration of thyroid tissue was noted. It would thus appear that whereas in some patients showing persistence the cause of the disease remains active in spite of thyroidectomy, in patients showing recurrence the cause becomes quiescent and after a variable period becomes active again. The course of the disease in patients with persistence and recurrence, in particular its tendency to show remissions and relapses in association with fluctuations in the rate of metabolism, resembles the course of the untreated disease. The problem that continues to puzzle us is why the cause of the disease should apparently become quiescent in such a large percentage of patients at the time of a subtotal thyroidectomy, thus permitting a cure.

TREATMENT

The effect of iodine on the course of the disease was determined in 33 of the 39 patients thyrotoxic after operation. In 22 the disease was controlled by administration of iodine either during the period of observation or until remission of the disease took place, after which no further treatment was necessary. In 11 patients the disease could not be controlled with iodine. That is, the basal metabolic rate remained at a level of + 15 per cent or higher in spite of prolonged administration of iodine. Six of these patients had second subtotal thyroidectomies, with termination of the thyrotoxicosis in 4. In 1 patient it is too soon after operation to tell whether the disease is still present or not, and 1 patient had a

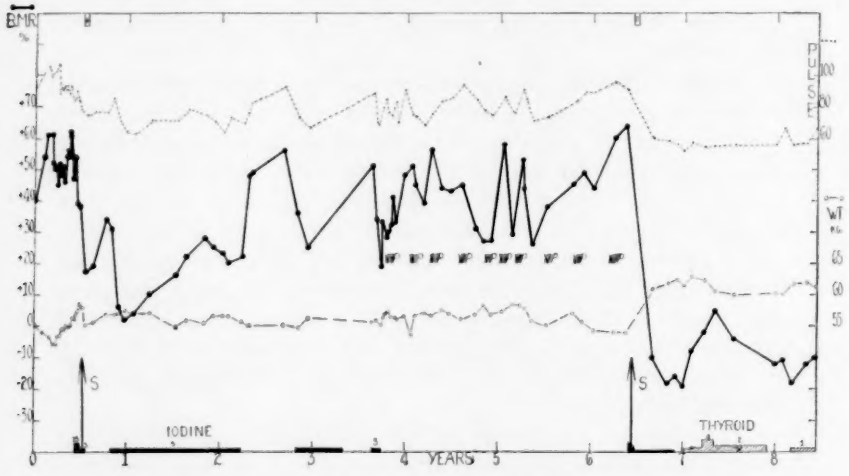

Chart 6 (patient 12).—Persistence of exophthalmic goiter, with a great deal of regeneration of thyroid tissue in spite of roentgen ray treatment over the pituitary and the administration of iodine. The patient became myxedematous after a second subtotal thyroidectomy. Symbols in center of chart which look like *XP* indicate roentgen ray treatment over the pituitary. For explanation of the other symbols see chart 1.

second persistence which lasted from three to four months and was then followed by a spontaneous remission. Of the 5 others in whom the disease could not be controlled with iodine, a second thyroidectomy was contraindicated in 1 because of vocal cord paralysis resulting from the first operation (patient 11). She was given roentgen ray therapy over the thyroid gland, with prompt and permanent remission. The other 4 patients have been advised to have a second thyroidectomy.

In general, in our experience, about two thirds of patients in whom thyrotoxicosis persists or recurs after operation require no treatment

other than the prolonged use of iodine to hold the disease in check or to control it until permanent remission takes place. In view of this relatively large percentage, iodine therapy should be given a fair trial in all patients. In about one third of the patients the disease cannot be controlled with iodine. Of 11 patients in this category, all but 1 showed marked regeneration of thyroid tissue. It is our practice under such circumstances to advise a second thyroidectomy. Roentgen ray therapy is reserved for those patients in whom some factor, such as paralysis of the recurrent laryngeal nerve on the unaffected side makes further surgical intervention inadvisable and for those who refuse to have further surgical treatment.

That in many patients thyrotoxicosis after operation can be controlled with iodine has received some attention. Berlin and Gargill [4] stated that they give it a fair trial in all patients except those in whom there is marked regeneration of thyroid tissue. Haines [11] found that of 488 patients with recurrent or persistent exophthalmic goiter who were examined at the Mayo Clinic, 123 (25 per cent) were treated satisfactorily with medical management only. In our own experience the disease was adequately controlled with iodine in a larger percentage of patients (about 67 per cent).

RESULTS OF SUBTOTAL THYROIDECTOMY IN VARIOUS CLINICS

In 1930 one of us (W. O. T.) and associates [1] pointed out that the incidence of thyrotoxicosis following subtotal thyroidectomy as reported from various clinics previous to that time varied from about 0.25 to 25 per cent, many of the reports showing an incidence of 5 to 7 per cent. It was pointed out that variations in these figures were in part due to the different types of follow-up study used by different authors.

It is of interest that the incidence of postoperative thyrotoxicosis among 190 patients with exophthalmic goiter followed at the Massachusetts General Hospital from 1920 to 1929 by Thompson, Morris and Thompson [1] was 19.5 per cent, practically the same as the incidence of 17.5 per cent for patients with exophthalmic goiter in the present series. The type of follow-up study used in both investigations was the same.

Of 4,956 patients with hyperthyroidism undergoing thyroidectomy from 1928 to 1937 at the Lahey Clinic, Boston, 2.4 per cent were operated on for persistence and 3.7 per cent for recurrence of the disease.[12] Joyce, in summarizing the results of thyroid surgery at the

11. Haines, S. F.: The Use of Iodine in Recurrent Exophthalmic Goiter, West. J. Surg. **42**:449-455 (Aug.) 1934.

12. Cattell, R. B., and Perkin, H. J.: Recurrent Hyperthyroidism, West. J. Surg. **47**:55-61 (Feb.) 1939. Cattell, R. B.: The Technic of Secondary Thyroidectomy for Recurrent or Persistent Hyperthyroidism, S. Clin. North America **19**:573-578 (June) 1939. Cattell and Morgan.[5]

Portland Clinic,[13] Portland, Ore., stated that the incidence of recurrence among patients operated on for goiter was 3.6 per cent for the adenomatous and 5.7 per cent for the hyperplastic variety. Of 108 patients operated on by Gillette,[14] 7, or 6.5 per cent, were reported to show recurrence. Buchbinder[15] reported that of 582 consecutive patients undergoing thyroidectomy by Dr. H. M. Richter, 3.3 per cent required a second operation. Young[16] found that 2.7 per cent of 2,064 patients required a second operation. In these reports the incidence of postoperative thyrotoxicosis is based on the number of patients requiring a second thyroidectomy. There were only 10 such patients in our series, all with exophthalmic goiter, so that if this was the only criterion of postoperative thyrotoxicosis the incidence would be reduced to 3.4 per cent. The incidence of postoperative thyrotoxicosis is much higher when patients are followed up for long periods with basal metabolism determinations and physical examinations, as in the present study. If left to their own judgment many patients still thyrotoxic after operation would feel so much better than before that they would consider themselves cured.

Hagen[17] estimated that the combined incidence of persistence and recurrence of the disease in a series of 500 patients whom he had operated on for toxic goiter was about 20 per cent. Bowers[9] reported the incidence of recurrence was 6.6 per cent among 302 patients with toxic goiter whom he had observed throughout the course of their illness. Coller and Potter[18] in a follow-up study, conducted partly by letter one to five years after operation, found an incidence of recurrence of 4.8 per cent among 267 patients with exophthalmic goiter and no recurrences among 273 patients with toxic adenoma. Hane,[19] after a follow-up study conducted by letter of 62 patients operated on for exophthalmic goiter, concluded that 3.2 per cent had recurrence and 4.8 per cent persistence of the disease. None of these authors specified the type of operation.

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13. Joyce, T. M.: Thyroid Surgery at the Portland Clinic, Ann. Surg. **94**: 563-567 (Oct.) 1931.

14. Gillette, N. W.: Recurrent Hyperthyroidism, West. J. Surg. **45**:504-510 (Sept.) 1937.

15. Buchbinder, W. C.: Some Cases of So-Called "Recurrent Thyrotoxicosis," M. Clin. North America **14**:1267-1276 (March) 1931.

16. Young, T. O.: Recurrent and Continuing Hyperthyroidism, Am. J. Surg. **39**:104-111 (Jan.) 1938.

17. Hagen, O. J.: Recurrent Thyrotoxicosis After Thyroidectomy, Minnesota Med. **22**:828-831 (Dec.) 1939.

18. Coller, F. A., and Potter, E. B.: The End Results of Thyroidectomy, Ann. Surg. **94**:568-581 (Oct.) 1931.

19. Hane, R. L.: Recurrent Hyperthyroidism, J. Indiana M. A. **33**:675-677 (Dec.) 1940.

Clarke and Black [20] recalled 181 patients two and a half years after operation for toxic goiter and found that in "44 per cent there was either a definite persistence or a recurrence of the condition," the patients not having obtained sufficient relief to consider themselves well. Of 171 patients followed by Pool and Garlock [21] for six months to nine years after resection of the thyroid gland in one stage for toxic goiter, 9.4 per cent had recurrences. Smith [22] found that 13 per cent of 75 patients with toxic diffuse goiter had hyperthyroidism after subtotal thyroidectomy. Of 804 patients followed six months to fourteen years after thyroidectomy for hyperthyroidism, McQuillen and Breidenback [23] considered 5.6 per cent to have recurrences, although some of the patients had a recurrence of the goiter only. In Berlin and Gargill's series [4] of 235 patients, all of whom had subtotal thyroidectomies, there were 3.0 per cent with persistence and 2.1 per cent with recurrence of the disease. In a five year follow-up study of 97 patients operated on for thyrotoxicosis at the Lahey Clinic Clute and Veal [24] reported that 6 had persistent and 6 recurrent thyrotoxicosis, a total incidence of postoperative thyrotoxicosis of 12.3 per cent.

Variations in these figures depend on the frequency and the type of the follow-up study and on the observer's evaluation of the patient when he sees him after operation. Unfortunately, a distinction is not made between persistence and recurrence of the disease in many reports. However, there seems to be general agreement that of all patients having subtotal thyroidectomy for toxic goiter, 2.7 to 6.5 per cent have severe enough postoperative thyrotoxicosis to require a second thyroidectomy.

COMMENT

It is of interest that in a group of patients with exophthalmic goiter studied in Chicago, an area in which simple goiter is prevalent, during the period 1930 to 1939, the incidence of postoperative thyrotoxicosis was about the same as that in a group of patients studied in Boston, an area in which simple goiter is rare, from 1920 to 1929. The surgeons performing the thyroidectomies in both series were probably about equally competent, suggesting that the cause of the thyrotoxicosis is not abolished by the

20. Clarke, N. E., and Black, I.: Postoperative Results in Toxic Goiter, Arch. Int. Med. **46**:266-282 (Aug.) 1930.

21. Pool, E. H., and Garlock, J. H.: The Surgical Treatment of Exophthalmic Goiter: Late End-Results, Surg., Gynec. & Obst. **59**:330-336 (Sept.) 1934.

22. Smith, M. K.: Amount of Thyroid Tissue to be Left in Operations for Diffuse Toxic Goiter, Ann. Surg. **108**:563-573 (Oct.) 1938.

23. McQuillen, A. S., and Breidenback, L.: Morbidity Following Goiter Operations, Ann. Surg. **106**:169-182 (Aug.) 1937.

24. Clute, H. M., and Veal, J. R.: The End-Results of Surgery in Exophthalmic Goiter, J. A. M. A. **99**:642-645 (Aug. 20) 1932.

operation and may continue to be active in spite of it. Both in the Chicago and in the Boston series, the incidence was lower among the patients of the more experienced surgeons than among those whose thyroidectomies were performed by less experienced surgeons. In general, the less experienced surgeons did less complete thyroidectomies. As the thyroidectomy becomes more and more complete, the gland becomes less and less capable of responding to any stimulus to which it may be subjected. The relation between the amount of thyroid tissue and the severity of the thyrotoxicosis is probably modified by the intensity with which the cause of the disease is acting. A few patients show definite persistence of the disease in spite of the presence of only a small amount of palpable thyroid tissue or no palpable tissue at all. That the cause of the disease is still active in patients showing persistence of exophthalmic goiter is also illustrated by the regeneration of thyroid tissue in a fairly large percentage of them. The surprising thing is that a subtotal thyroidectomy ever cures exophthalmic goiter, and yet in over 80 per cent of cases the basal metabolic rate drops to normal or below after this procedure and remains there. In some instances a hemithyroidectomy may cause reduction of the basal metabolic rate to normal. Thus there appears to be a balance of the intensity with which the cause of the disease is acting, the amount of thyroid tissue and the production of active agent by the gland. Exacerbations may occur in the degree to which the cause is acting. Only in this way can recurrence and variations in the intensity of persistence of thyrotoxicosis be explained.

SUMMARY AND CONCLUSIONS

Of 294 patients with toxic goiter undergoing subtotal thyroidectomies during the period 1930 to 1939 and followed up from three months to ten years after operation, 39 showed definite clinical evidence of postoperative thyrotoxicosis. Of this number, 37 were among 212 patients with exophthalmic goiter (17.5 per cent) and 2 among 82 patients with toxic adenoma (2.4 per cent).

The thyrotoxicosis was usually less severe than before operation, although in 3 patients it was more severe.

Distinction is made between persistent and recurrent thyrotoxicosis. In 30 patients the thyrotoxicosis was persistent and in 5 recurrent, while in 4 patients the type could not be determined.

In 3 of the 5 patients considered to have recurrent thyrotoxicosis the recurrence was preceded by a persistence and a spontaneous remission of the disease.

In 22 of 33 patients on whom the observation was made it was found that postoperative thyrotoxicosis could be adequately controlled with

iodine alone. In 11 of these patients who had a persistence of the disease, permanent remission was observed between four months and three years after operation.

There was a rough parallelism between the amount of thyroid tissue palpable after operation and the degree of postoperative thyrotoxicosis, although there were important exceptions to this rule. Thus regeneration of thyroid tissue was observed in 74 per cent of patients with postoperative thyrotoxicosis but in only 15 per cent of those without thyrotoxicosis after operation. Of the patients as a whole, regeneration was observed in 22 per cent.

The presence of palpable thyroid tissue after operation is evidence in favor of thyrotoxicosis until proved otherwise.

Two main factors are responsible for thyrotoxicosis following subtotal thyroidectomy for toxic goiter: (1) the failure of the operation to remove the cause of the disease, and (2) the removal of too little thyroid tissue.

Such factors as infections, pregnancy, the menopausal syndrome, worry and fatigue do not seem to play an important role. If related in any way to the onset of the disease, they are certainly no more than precipitating factors.

It is probably desirable to reoperate on all patients with postoperative thyrotoxicosis in whom the basal metabolic rate cannot be held at or near the standard normal level (below + 15 per cent) by the administration of iodine.

Postoperative administration of iodine will not prevent the regeneration of thyroid tissue.

The course of postoperative thyrotoxicosis, including its tendency toward remissions and relapses, resembles the course of the untreated disease.

CARDIOMETRIC STUDIES ON CHILDREN

III. REPORT OF A CASE OF INCOMPLETE HEART BLOCK DUE TO VAGAL EFFECT *

WILLIAM POEL

BETHESDA, MD.

Reports on persistent vagal disturbances of the heart mechanism in apparently normal persons with the exception of sinus arrythmia and bradycardia are exceedingly rare. A survey of the literature revealed only 3 cases of such disturbance.[1]

In a recent study of the electrocardiographic variations of the healthy heart, electrocardiograms and stethograms were made on more than 2,400 apparently normal high school students. The following case of physiologic heart block of vagal origin was the only instance of such a disturbance which was observed. It occurred in a Negro boy who except for this abnormality was clinically normal and entirely free of any sense of physical ill-being or of symptoms which could be related either directly or indirectly to a condition of heart block. Observations made in this case are reported, compared with those of Levy [1a] and Marzahn [1b] and discussed in the light of electrocardiographic changes in the human heart due to experimentally induced vagal effects.[2]

REPORT OF CASE

History.—According to his medical history, a Negro boy aged 15 had never suffered from attacks of rheumatic fever, chorea or heart disease. He had received

* Data on which this paper is based were derived from a cooperative investigation by the United States Public Health Service, Division of Public Health Methods; the Cornell University Medical College, Departments of Public Health, Preventive Medicine and Pediatrics; the Milbank Memorial Fund, and the New York City Department of Health. The cooperating agencies have been assisted in carrying out this investigation by the Work Projects Administration for the city of New York, Official Project No. 65-1-97-21, W. P. 24, "Medical Evaluation of Nutritional Status."

1. (*a*) Levy, R. L.: Partial Heart Block Due to Increased Vagus Action, Ann. Int. Med. **12**:1525-1529 (March) 1939. (*b*) Marzahn, H.: Clinical Notes on the Question of Functional Heart Block, Klin. Wchnschr. **15**:486-488 (April 4) 1936.

2. (*a*) Robinson, G. C., and Draper, G.: Studies with the Electrocardiograph on the Action of the Vagus Nerve on the Human Heart. J. Exper. Med. **14**:217-233, 1911. (*b*) Sigler, L. H.: Electrocardiographic Observation on the Carotid Sinus Reflex, Am. Heart J. **9**:782-791 (Aug.) 1934. (*c*) Wiggers, C. J.: Physiology in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1937, p. 468.

periodic physical check-ups from his father, who is a physician. He had never experienced spells of dizziness, fainting, palpitation of the heart or other symptoms which might be traceable to cardiac dysfunction. At the time of the survey the boy was a member of his school's swimming team. He had always been an active athlete.

Physical Examination.—Routine examination revealed the boy to be well nourished and well developed. The stage of physical development was advanced adolescence. The eyes, ears, nose and mouth showed nothing abnormal. The tonsils were normal, and the thyroid was not enlarged. No lymph nodes were palpable. The lungs were normal. The blood pressure was 120 systolic and 80

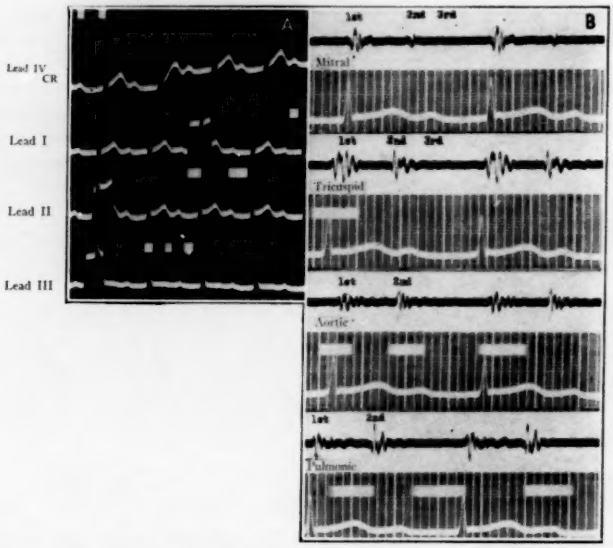

Fig. 1.—*A*, routine electrocardiogram taken on March 21, 1940. The only abnormality in the record is the prolonged PR interval measuring 0.36 second in lead IV. Lead IV_{CR}, the routine fourth lead used in this study, was taken with the lead selector on lead I, employing the right arm electrode and cable on the right arm and the left arm cable and precordial electrode on the precordium. *B*, routine stethogram taken March 21, 1940. The sounds are all of normal contour and duration. A third heart sound is recorded on the tracings from the mitral and the tricuspid area. This sound is recorded at the latter area with greater clarity than it is at the former area.[4] A fine systolic vibration of low intensity is recorded at the mitral, the pulmonic and, intermittently, the aortic area. This vibration can be identified as the fine "saw tooth" ripple of the base line between the first and second sounds (compare figure 5).

diastolic, with a pulse rate of 60 per minute with the boy in the lying position. The apical impulse was felt 8.5 cm. from the midsternal line in the fifth intercostal space. No systolic or diastolic murmurs were heard. The heart sounds were normal.

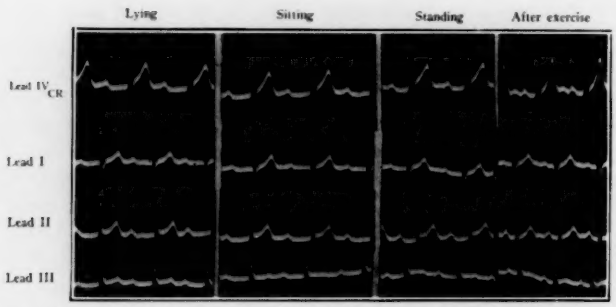

Fig. 2.—Electrocardiogram taken on May 27, 1940 to show the effect of various positions and exercise. As the subject passes from a resting to an active state voltage changes occur, an S wave appears in lead II and the ST segment in lead II is lowered. The PR intervals shorten from 0.36 second with the subject in the lying position to 0.34 second as he assumes the sitting position, then to 0.28 second as he stands erect and finally to 0.19 after he exercises.

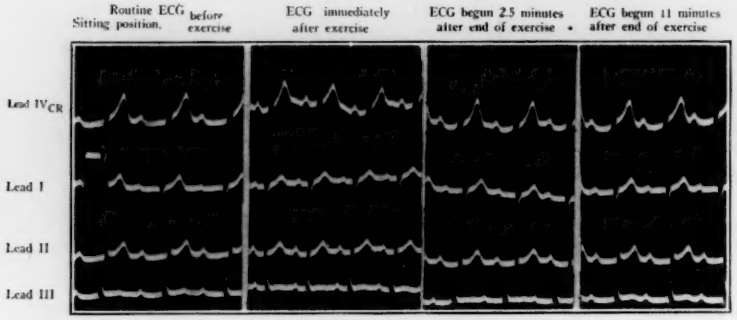

Fig. 3.—Electrocardiogram taken on Nov. 26, 1940, with the subject in the sitting position and the leads recorded in the following sequence: IV, I, II and III. The elapsed time between the beginning of one lead and the beginning of the sequential lead was 0.5 minute. Thus, for example, lead III of the series begun 11 minutes after the end of the exercise was actually recorded 12.5 minutes after the end of exercise.

The change in duration of the PR interval in lead IV is from 0.40 second before exercise to 0.18 second immediately after exercise. This is almost identical with the change recorded on May 27. The gradual elongation of the PR interval to its original value before exercise is shown in the tracings begun 2.5 minutes and 11 minutes after exercise. The PR interval in lead III, taken 12.5 minutes after exercise, had a duration of 0.34 second. This value, peculiarly, is greater than the 0.32 second for the PR interval in lead III recorded before exercise. Changes in the voltage of the S wave in lead II and the depression of the ST segment in lead II, which were brought on by exercise, are also seen to disappear 12 minutes after exercise.

Laboratory Data.—The Wassermann reaction of the blood was negative. Urinalysis, chemical studies of the blood and hematologic examination revealed nothing abnormal. Anterior-posterior and lateral roentgenograms and roentgen kymograms were taken before and after exercise. They revealed a heart of normal contour and dimensions.

Electrocardiographic and Stethographic Examination.—Method: The first electrocardiogram and stethogram were taken on March 21, 1940, with the boy in the sitting position (fig. 1 *A* and *B*).

The routine precordial lead (IV_{CR}) was made with the precordial electrode and left arm cable on the precordium and the right arm electrode and cable on the right arm, with the lead selector on lead I. This method of taking lead IV_{CR} yields the same recording as is obtained by employing the method suggested by the American Heart Association. However, in comparison with the latter method, it has the distinct advantage of insuring greater speed and greater accuracy on the part of the technician.

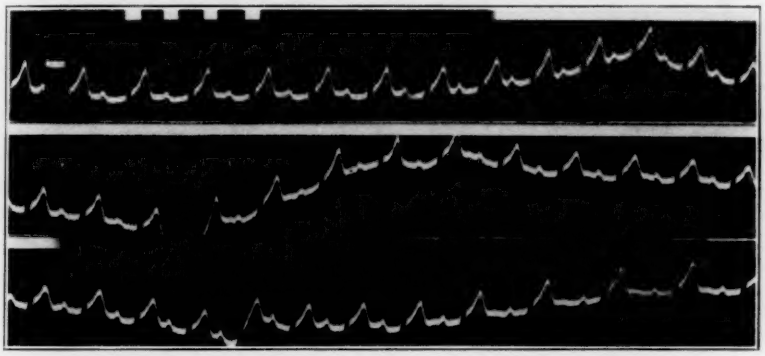

Fig. 4.—Electrocardiogram taken on Nov. 26, 1940 to show the effect of a deep, sustained inspiration on the PR interval. The three sections represent a continuous tracing. The four short white dashes at the beginning of the tracing (section 1) identify the lead employed (IV_{CR}). The long white dash, beginning approximately 3 seconds later (section 1) and extending through to the beginning of the third section, marks the start, duration and end of a single deep inspiration. Measurements of the PR interval show that it varies from 0.31 to 0.34 second during normal respiration (the part of section 1 preceding the long white dash). For the duration of the sustained inspiration the PR interval varies from 0.26 to 0.30 second. In the third section, after the end of the dash and the resumption of normal respiration, the PR interval varies from 0.27 to 0.30 second.

The findings in the fourth lead are used throughout in describing the changes which form the basis of this report. This is done because no significant variation in the PR interval occurs in the different leads and the waves and complexes are recorded with greater clarity and amplitude in lead IV_{CR} than they are in the standard leads.

Heart sound tracings were taken at the mitral, tricuspid, aortic and pulmonic areas.[3] Respiration was suspended at the end of a normal expiration while the

3. A Sanborn Stetho Cardiette was employed throughout the study.

records were made. The mitral and tricuspid tracings in this case were both taken at the volume amplification of 4.2 on the instrument's arbitrary scale of volume setting; the aortic and pulmonic tracings were taken at the volume setting of 4.9. Lead II was run simultaneously with every sound recording.

Electrocardiographic Findings: The heart rate was recorded as 81.

The only abnormality noted in the record is a prolonged PR interval, measuring 0.36 second in lead IV. The variation in the PR interval of successive cycles in each lead was at no time greater than 0.02 second (fig. 1 *A*).

Diagnosis: The diagnosis was a marked degree of incomplete heart block.

Stethographic Findings: The vibrations of the heart sounds are of normal contour and duration at all areas (fig. 1 *B*). A perceptible systolic murmur is recorded at the mitral and the pulmonic area. (No murmur was heard by the physician who did the routine physical examination.)

A vibration of low frequency and low amplitude is visible after the second heart sound at the mitral and the tricuspid area. The position of this vibration in the diastolic phase suggests at first that it may be a third heart sound. However, this vibration shows a slightly more constant time relation to the P wave of the electrocardiogram than it does to the second heart sound of the stethogram. Furthermore, it is of greater amplitude at the tricuspid than at the mitral area (fig. 1 *B*). It is, therefore, more probable that this vibration represents a summation of the normal third heart sound and the auricular systolic rather than the third heart sound alone.[4]

Special Observations.—Because of the unusually long PR interval, the absence of dropped beats and the completely negative case history and physical examination, the boy was reexamined on May 27 and on November 26.

On May 27 electrocardiograms were made with the boy in the lying position after a rest period of 10 minutes; in the sitting and the standing position, and in the standing position after exercise. Figure 2 and the table show certain of the results obtained.

The outstanding features are tabulated as follows:

Position	Calculated Heart Rate, per Minute	Duration of PR_{IV}, Second
Lying	75	0.35-0.38
Sitting	74	0.32-0.34
Standing	74	0.28-0.31
Standing After Exercise	90	0.18-0.19

4. Third heart sounds are infrequently observed. They are usually recordable at the mitral area only, rarely at the tricuspid area (Boone, B. R., and Ciocco, A.: Cardiometric Studies on Children: I. Stethographic Patterns of Heart Sounds Observed in 1482 Children, Milbank Mem. Fund Quart. **17**:323-357, 1939; II. The Duration of the Component Parts of the Cardiac Sound Cycle, ibid. **18**:137-155, 1940). When they are recorded at the latter area, the amplitude is always much lower. In this case the vibration in question on the tracing taken over the tricuspid area March 21, 1940 was recorded with an amplitude equal to, if not greater than, the amplitude of this vibration on the tracing taken over the mitral area (fig. 1 *B*). Furthermore, as has already been mentioned, there is some variation in the interval between this diastolic wave and the preceding second heart sound. The variation seems to depend on the occurrence of the P wave immediately preceding this diastolic vibration on the stethogram. It is therefore believed that the vibration represents a ventricular thud produced by the rush of blood into the ventricles during the period of rapid ventricular filling which is augmented by an auricular systole.

On November 26 electrocardiograms and stethograms were again taken (figs. 3 through 6 and table). The control electrocardiogram taken with the boy in the sitting position showed practically no variation, as compared with the preceding control graphs, except that the PR interval in lead IV was 0.38 to 0.40 second in duration. Immediately after exercise, this interval was 0.18 to 0.20 second. Two and a half minutes after the end of exercise the PR interval had increased to 0.26 to 0.28 second. After 11 minutes it showed a further increase to 0.31 second (fig. 3).

The effect of deep sustained inspiration on the PR interval was investigated, as shown by figure 4. A continuous tracing (lead IV_{CR}) was taken before, during

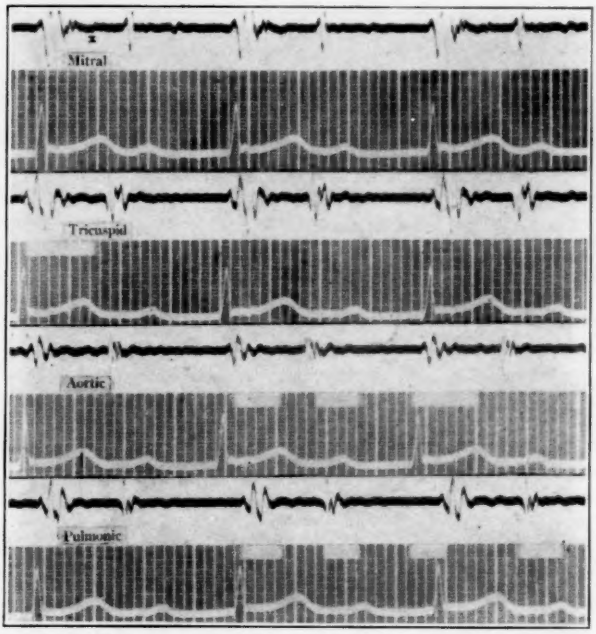

Fig. 5.—Stethogram taken on Nov. 26, 1940, showing an intermittent third heart sound recorded at the tricuspid area. The vibration appears clearly only in the last cycle of the record. (The vibration has a more constant character in figure 1 *B* in the tracing recorded at the tricuspid area.)

Further comparison of figure 5 with figure 1 *B* reveals the disappearance of the systolic vibrations previously recorded at the pulmonic zone. The systolic intervals of the pulmonic tracing in this figure are just as smooth as are the diastolic intervals. The series of fine systolic vibrations seen on the mitral tracing of figure 1 *B* are replaced in this figure by a single vibration (*x*) of low amplitude. Such vibrations are always visible in the electrocardiograms of persons who have an "intrasystolic click." Their significance here is uncertain. The variation was inaudible to the observer at the time the tracing was made.

and after a deep inspiration, which was held for 14 seconds. The PR interval during the 6 seconds preceding the beginning of the deep inspiration varies from 0.31 to 0.34 second (fig. 4—from the beginning of the tracing to the beginning of the white dash following the lead marks). During the deep breath (sustained from the PR interval preceding the white dash till the end of the dash) the PR interval varies from 0.26 to 0.30 second. Immediately after the end of inspiration and for the following 11 seconds the PR interval varies from 0.27 to 0.30 second.

It is therefore obvious that holding the breath after a deep inspiration had a slight but definite effect in shortening the PR interval. This observation is not in

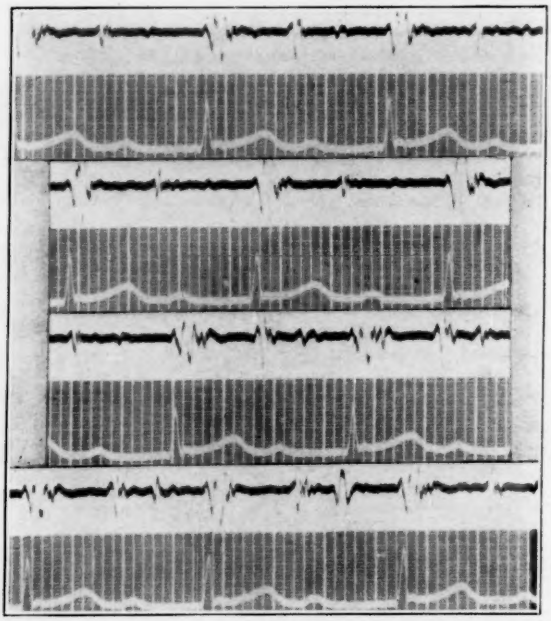

Fig. 6.—Stethogram taken on Nov. 26, 1940 to show the effect of respiration on the mid-diastolic vibration, or third heart sound. The four sections represent a continuous tracing. The subject suspended respiration for a few seconds after a normal expiration. Breathing was resumed during the diastole of the second heart cycle of section 1 (as shown by the disturbed base line). The third heart sound was inaudible throughout sections 1 and 2 and during part of section 3. It became audible in the last cycle of section 3 and reached its greatest intensity in section 4. The last cycle of section 4 shows the vibration reduced to its usual subaudible amplitude. This tracing was recorded at the mitral area.

agreement with that of Levy, who stated that in the subject whose case he reported a sustained inspiration induced the Wenckebach phenomenon, a condition equivalent to an increased auriculoventricular block.

Comparison of Data in Four Cases of Incomplete Heart Block Due to Vagal Effect

Author	Marzahn,[1b] case 1	Marzahn,[1b] case 2	Levy [1a]	Poel (case reported here)
Age	32 years	24 years	14 years	15 years
Complaints	Stitches and occasional pain in heart ever since an accident	Systolic murmur at apex; spastic constipation	Frequent fainting spells	None
Type of subject	Robust	Lean; athletic	Thin; undernourished	Lean; well nourished; athletic
Clinical observation	Irregularity of heart beat	No abnormalities	Intermittence of pulse	No abnormalities
Roentgen examination of heart	Normal	Normal	Bulging in region of pulmonary conus	Normal
Stethoscopic examination of heart	Not given	Not given	Occasional occurrence of a soft blowing systolic murmur at the pulmonic area	No murmurs
Condition of heart	Organically sound	Organically sound	Organically sound	Organically sound
Control electrocardiogram	Rate = 70; partial 2:1 sinoauricular block; no conduction delay	Rate = 80; incomplete auriculoventricular block; PR = 0.25 sec.	Rate = 86; second degree heart block; PR = 0.26 sec.	Rate = 81; incomplete auriculoventricular block; PR = 0.36 sec.
Effect of holding a deep breath	Not given	Not given	Rate = 79; Wenckebach phenomenon occurred	Rate change insignificant; PR reduced from 0.33 to 0.28 sec.
Effect of exercise	Rate = 120; PR = 0.12 sec.; regular sinus rhythm; no dropped beats	PR reduced to 0.20 sec.	Rate = 86; PR = 0.18 sec.; no dropped beats	Rate = 90; PR = 0.18 sec.
Effect of digitalis	Not given	Not given	Increase of auriculoventricular block	Not tried
Effect of atropine	Rate = 108; disappearance of dropped beats	PR = 0.15 sec.; auriculoventricular nodal rhythm induced	Auriculoventricular block abolished	Not tried
Effect of position of patient on electrocardiogram	Not given	Not given	Not given	PR longest in lying position (0.36 sec.), shortest in standing position (0.30 sec.)
Electrocardiographic variations exclusive of those induced by above means	Not given	Spontaneous variation of PR interval from 0.18 to 0.35 sec. from day to day	No variation noted	PR interval shortened to 0.18 sec. by exercise; gradual reversion to original duration after exercise
Stethographic examination of heart	Not given	Not given	Not given	Inaudible auricular (or third) heart sound recorded at mitral area; sound markedly accentuated and audible when beating resumed after short periods of suspended respiration

An unusual variation in intensity and audibility of the diastolic vibration (or third heart sound) was heard stethoscopically at the time the effect of deep breathing was investigated. During normal respiration the vibration of this third heart sound could be observed visually by means of the stethographic galvanometer. It reached an audible intensity only occasionally, at which time it was heard as a soft, dull, thudlike sound. The control stethogram was taken with respiration suspended at the end of a normal expiration, during which time the diastolic vibration was inaudible. When respiration was resumed by the subject the intensity and audibility of this diastolic vibration showed a marked increase soon after the first inspiration. It reached an audible intensity, remained there for a number of cycles and then diminished to its usual level. A stethogram was taken to illustrate the phenomenon (fig. 6). The subject began to inhale after the second heart sound of the second cycle. The third heart sound became audible in the seventh cycle.

The table summarizes the comparable data in this case and in cases of similar disturbance recorded in the literature.

COMMENT

Since all clinical and laboratory findings appeared to show a normal cardiovascular system, the electrocardiographic data obtained were interpreted as indicative of a persistent auriculoventricular heart block due to vagal influence.

A review of the literature revealed that both auriculoventricular and sinoauricular heart block have been produced experimentally by stimulation of the vagus nerve. Robinson and Draper,[2a] in 1911, reported that stimulation of the right vagus nerve by pressure in a man with an anatomically normal heart had a more marked effect on the rate of the heart than had stimulation of the left vagus nerve. Stimulation of the latter seemed to have a more marked effect on the conduction of the cardiac stimulus from auricles to ventricles. Sigler [2b] reported the predominant vagal effects on the heart obtained on carotid sinus pressure to be sinoauricular slowing, or standstill, as well as various grades of auriculoventricular block. He found that pressure on the right carotid sinus had a greater tendency to produce complete standstill, whereas pressure on the left one had a greater tendency to produce complete auriculoventricular block. This he explained by stating that although terminal branches of both vagus nerves are present in each node, right vagal terminals are found in greater number in the sinus node, while left vagal terminals predominate in the auriculoventricular node. Wiggers' [2c] findings were in accord with those of Sigler. He stated that some vagal fibers from the right branch terminate in the sinoauricular node, decreasing its rate of discharge and consequently slowing the heart. He explained functional heart block produced by stimulation of the left

vagus nerve as due to those fibers from the left branch which connect with the auriculoventricular node and junctional tissue and act either by extending the refractory period or by decreasing the conductivity of the tissue in which they end. In this way heart block is produced which may range from slight delay of conduction to complete blockage of the impulse to the ventricle.

Thus, in the majority of cases vagal influence on the cardiac mechanism has been reported to result in (1) interference with the impulse formation in the sinoauricular node (when the right vagus nerve is stimulated), (2) interference with the conduction of the sinus impulse along the auriculoventricular junctional tissue and node (when the left vagus nerve is stimulated) or (3) varying degrees both of sinoauricular and of auriculoventricular nodal interference (if a generalized high vagal tone involving both vagus nerves is induced).

By viewing the case presented here and those previously reported in the light of the laboratory observations just mentioned, it would appear that the experimental data may be considered as a medium, or matrix, which brings together and provides a basis for relating the 4 cases summarized in the table. Conversely, it can be seen that these cases may represent instances of the spontaneous occurrence in apparently normal persons of conditions previously elicited only under experimental conditions.

Experimentally, the electrocardiographic abnormality seen in figure 1 *A* has been induced by other investigators, by stimulating the left vagus nerve. Thus, in the case presented here, in which there is no sign of sinoauricular nodal depression, no clinical or other abnormality is apparent and the only abnormal finding is a markedly prolonged PR interval, the origin may be explained by assuming that an activating agent producing a high vagal tone is present somewhere along the path of that branch of the vagus the fibers of which predominate in the region of the auriculoventricular node.

SUMMARY

A case of persistent functional heart block apparently due to vagal influence is presented. Three previously described cases of such disturbance are reviewed.

The frequency of occurrence of this phenomenon in normal adolescents is low. It was encountered only once in 2,400 electrocardiograms made on normal persons between the ages of 12 and 20.

Body position, body activity and respiration were found to have a definite effect on the duration of the PR interval in the case reported

here. Respiration also affected the intensity and audibility of a third heart sound, or auricular sound.

Observations pertaining to the effect on the heart of experimental excitation of the vagus nerve are reviewed. A possible explanation of the origin of functional heart block is suggested in the light of these observations.

Dr. C. E. Palmer, Division of Public Health Methods, National Institute of Health, and Dr. William Schmidt, medical director of the cooperative nutrition study, aided me in preparing this report and reviewed it before publication. Dr. Frank Liberson, radiologist, United States Public Health Service, made the roentgenograms, and Dr. Harry Gold, Cornell University Medical College, read the manuscript. Miss Carmeta Scott aided in preparing the manuscript.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

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(Concluded from p. 926)

INFECTIOUS MONONUCLEOSIS

Since the observation of Murray, Webb and Swann in 1926 that organisms of the genus Listerella (Bacterium monocytogenes) could produce mononucleosis in rabbits, there has been speculation as to their possible etiologic relation to infectious mononucleosis in human beings. The evidence as to the importance of this organism in relation to the disease is conflicting. This is because in only a small proportion of cases can it be cultivated from the blood and the spinal fluid and because it has not been demonstrated that antibodies against organisms of this group develop in the serum of patients with infectious mononucleosis. Janeway and Dammin [209] undertook a study to ascertain whether in patients with infectious mononucleosis agglutinins develop for either of the two known serologic groups of the genus Listerella. They observed that in all but 3 members of the normal control group the results of the sheep cell agglutination test fell within the normal range given by most authors, namely, agglutination in a final dilution of 1:64 or less. These 3 exceptions occurred in the serum of patients who had received horse serum for the treatment of pneumonia, and the highest titer, 1:1,024, was recorded in a patient with serum disease. The authors emphasize that it has been known for some time that the injection of horse serum will lead to the production of "heterophile" antibodies. The results of the Listerella agglutination tests showed a slightly elevated

209. Janeway, C. A., and Dammin, G. J.: Studies on Infectious Mononucleosis: The Relationship of the Organism of the Genus Listerella to the Disease, as Studied by the Agglutination Reaction, J. Clin. Investigation **20**:233, 1941.

titer in the serum of the patients with infectious mononucleosis as compared to that in the serum of the control groups, but there was no significant trend upward or downward in the Listerella agglutinin titer during the course of the disease or recovery from it. From these observations it was concluded that the study did not suggest any definite etiologic relation between the known Listerella organisms and infectious mononucleosis.

Sundberg [210] presents one of the most complete general articles dealing with infectious mononucleosis that has been published recently, and excellent photomicrographs of the infectious mononucleosis type of cell are reproduced. The author believes that blood studies afford the best basis for a diagnosis of the disorder, since the clinical manifestations may be varied and may simulate those of other conditions. In her opinion, the heterophile antibody test, which usually gives a positive reaction in the presence of the disease, is of great value, but it is not absolutely necessary for the diagnosis. The serious nature of some of the diseases with which infectious mononucleosis may be confused is emphasized, and for this reason the importance of an accurate diagnosis is stressed.

Barber [211] considers that infectious mononucleosis is probably a virus disease, fairly common in occurrence and of well recognized epidemiologic character. In 3 of his patients with the disease the outstanding feature was ulceration of the tonsils which was remarkably resistant to all forms of therapy.

It is emphasized by Werlin, Dolgopol and Stern [212] that infectious mononucleosis is of relatively frequent occurrence but that the disease is often not recognized. It may be confused with diphtheria, epidemic parotitis (mumps), follicular tonsillitis, streptococcic pharyngitis, sinusitis and various other infections. A general description of the syndrome is given. The authors state that the highest leukocyte count is observed during the first week of illness in children and during the second week of illness in adults. The heterophile antibody reaction was posititve in 90 per cent of their series of cases. According to their experience, the titer of serum showing a positive heterophile antibody reaction remains constant for months if the serum is stored in an ice box. The suggestion is made that serum giving a positive reaction be used as a control in performing the test with serum the reaction of which is unknown.

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210. Sundberg, D.: Infectious Mononucleosis, Detroit M. News, Educ. Issue **32**:29, 1941.

211. Barber, H. S.: Anginose Glandular Fever, Lancet, **1**:71, 1941.

212. Werlin, S. J.; Dolgopol, V. B., and Stern, M. E.: Infectious Mononucleosis—Diagnostic Problem, Am. J. M. Sc. **201**:474, 1941.

Mayer [213] presents a general article dealing with all aspects of the syndrome of acute infectious mononucleosis. A description of the clinical picture of infectious mononucleosis with special reference to cerebral complications is given by Thelander and Shaw.[214] They present a comprehensive résumé of present knowledge of all aspects of the disease. It is stressed that headache is the symptom referable to the nervous system which is common to all patients. Other manifestations are variable. There may be evidence of encephalitis with difficulty in speech, sluggishness and some mental confusion. Ptosis may be present. Evidence of meningitis with stiffness of the neck is, however, the most common sign of involvement of the nervous system. There is usually a moderate increase in the number of cells in the spinal fluid, averaging 50 to 80 per cubic millimeter, but the number may be as great as 600 or more. The exact pathologic changes in the nervous system are still obscure, but it appears from the authors' observations that there may be involvement of the brain or of the meninges or possibly of both. To date there has been no record of late sequelae. A case of infectious mononucleosis in which the manifestations in the nervous system were outstanding is reported by Landes, Reich and Perlow.[215] They emphasize that involvement of the nervous system is regarded as rare in this disease, but this is not entirely correct, as undoubtedly the true diagnosis is overlooked in some instances. This occurs especially in patients in whom the symptoms referable to the nervous system are recognized for as long as two weeks prior to the appearance of the lymphadenopathy. Usually headache and evidences of meningeal irritation, such as positive Kernig and Brudzinski signs, nausea and vomiting, are present. It is stated that characteristically the symptoms and signs referable to the nervous system disappear, with no residuum. The changes in the spinal fluid are neither diagnostic nor constant. The pressure may be elevated, and pleocytosis is variable, usually with a cell count of 25 to 300, largely lymphocytes. The total protein may be increased, as well as the globulin fraction. The Wassermann reaction and the colloidal gold curve of the spinal fluid are negative. Apparently, observations on the heterophile antibody reaction of the spinal fluid have not been previously reported; in this case the reaction was negative. The presenting clinical picture in this case was acute ataxia with an outspoken involvement of the

213. Mayer, O. B.: Acute Infectious Mononucleosis, J. South Carolina M. A. **37**:48, 1941.

214. Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis with Special Reference to Cerebral Complications, Am. J. Dis. Child. **61**:1131 (June) 1941.

215. Landes, R.; Reich, J. P., and Perlow, S.: Central Nervous System Manifestations of Infectious Mononucleosis: Report of a Case, J. A. M. A. **116**:2482 (May 31) 1941.

cerebellar system. In the opinion of the authors, the pathologic process, regardless of whether it should be regarded as encephalitis or toxic encephalopathy, extended over a considerable portion of the brain. As the lymphadenopathy and splenomegaly did not appear until twenty-two days after the onset of the symptoms, the diagnosis would probably have been missed except for the positive heterophile antibody reaction (1:2,048). They emphasize that this test should be employed in all cases in which there are acute and obscure cerebral symptoms.

According to Smith,[216] two types of conditions are encountered in young patients which are characterized by lymphocytosis and are consequently frequently confused with infectious mononucleosis or even with leukemia. In one type there is a transient, unexpected hyperleukocytosis with an absolute and a relative increase in lymphocytes which is unassociated with recognizable symptoms or physical signs. The second type, which is more frequently encountered, follows infections of the upper respiratory tract of varying intensity. It is characterized by fever of low grade, present for weeks or months, and associated symptoms, which frequently include anorexia, pallor, fatigability and paraumbilical pain. In both conditions there is a preponderance of lymphocytes in the blood with a normal or a moderate elevation of the cell count. These two syndromes are classified as acute and chronic infectious lymphocytosis and are differentiated clinically, hematologically and serologically from infectious mononucleosis, leukemia and miscellaneous infections commonly associated with lymphocytosis. The heterophile antibody reaction in patients with either condition is negative, and the bone marrow shows only an increase in the lymphocytes. Two cases of the first type, which the author designates as acute infectious lymphocytosis, were encountered in children 3½ and 6 years of age. The leukocyte counts were 92,000 and 44,300 per cubic millimeter and the lymphocyte percentages reached 86 and 79, respectively. The course of illness in each child was benign, and in neither was there lymphadenopathy, enlargement of the spleen or the clinical or physical signs characteristic either of infectious mononucleosis or of leukemia. The results of examination of sternal marrow ruled out leukemia, and the blood picture could be readily differentiated from that of infectious mononucleosis or leukemia. In neither instance did the heterophile antibody test give a positive result. (We call attention to an article by Reyersbach and Lenert, abstracted in this section, in which an apparently similar syndrome was regarded as infectious mononucleosis.) The second type occurs most commonly in infants and in young children and is frequently encountered in pediatric practice. This group includes cases in which

216. Smith, C. H.: Infectious Lymphocytosis, Am. J. Dis. Child. **62**:231 (Aug.) 1941.

after an infection of the upper respiratory tract a low grade fever continues to be present for prolonged intervals. Associated symptoms are those usually observed in any mild chronic infection. The blood in such cases shows moderate leukocytosis with an increased lymphocytic percentage instead of the anticipated neutrophilic response. The total leukocyte count in these cases varies from slightly above normal to 18,000 or 20,000 per cubic millimeter, and the lymphocytes are commonly found to comprise 70 to 80 per cent of the white cells. In neither type of the disease is there a significant decrease in the number of red cells or in the hemoglobin content. The author considers that acute and chronic infectious lymphocytosis may represent separate entities, although there is some evidence that they may be related. It is his belief that the etiologic agent of each type is probably an undetermined virus which is related to infection of the upper respiratory tract.

An important study is reported by Reyersbach and Lenert,[217] who observed 16 cases of what was regarded as atypical infectious mononucleosis in a group of 108 children who were receiving convalescent care for rheumatic fever. According to the authors, the outbreak of the disease differed from any other hitherto reported in that none of the children had symptoms or physical signs of any kind. The condition was discovered accidentally because examination of the blood was done at regular intervals as part of the general medical care. The maximum leukocyte counts of the 16 children varied from 18,400 to 59,300 cells per cubic millimeter, and the proportion of lymphocytes rose to a maximum of 93 per cent and was never lower than 71 per cent at the height of the disease. The predominating cell was of the normal small lymphocytic type. The large lymphocytes typical of infectious mononucleosis were not present. The heterophile antibody test in each instance gave a negative reaction, as did the Wassermann test which was done in 5 cases. The condition may be regarded as acute infectious lymphocytosis of the type reported by Smith and discussed in the preceding paragraph.

Fuller [218] reports 5 cases in which the patients had all of the more important clinical features of infectious mononucleosis except that the heterophile antibody reaction was positive in such a low titer (below 1 : 80) in 4 cases that it was not considered diagnostic. The test was not done in 1 case. The author concludes that if a positive heterophile antibody reaction is essential for the diagnosis of infectious mononucleosis, some other unknown factor appears to be capable of producing mononucleosis with a secondary infection of the throat and a generalized

217. Reyersbach, G., and Lenert, T. F.: Infectious Mononucleosis Without Clinical Signs or Symptoms, Am. J. Dis. Child. **61**:237 (Feb.) 1941.

218. Fuller, C. J.: Angina of the Throat Associated with Mononucleosis, Lancet **1**:69, 1941.

hyperplasia of the lymphoid tissues. The differential diagnosis of the condition reported and acute leukemia, agranulocytosis and diphtheria is discussed.

Warren [219] considers that the changes in the white cells and the serologic reactions are the two characteristic manifestations which differentiate the entity of infectious mononucleosis from other disorders presenting a similar clinical picture. The author has investigated the question of why the typical abnormal white cells of infectious mononucleosis may be present without an elevated heterophile titer. It is concluded that the Forssman heterophile antibodies are probably increased prior to the development of the antibodies of this disease and possibly are essential to their appearance. The typical lymphocytes of infectious mononucleosis are frequently found in disease conditions in which a positive Paul-Bunnell reaction has not been obtained. Only when these cells are present in considerable numbers does the elevated heterophile titer develop.

Barrett [220] believes that the lack of agreement concerning the percentage of cases of infectious mononucleosis in which sheep cell agglutination occurs is due, among other possible causes, to the unwitting use by different workers of various standards in the performance of the test. From his studies it is concluded that sheep cell titers of 1:80 and horse cell titers exceeding 1:320 should be regarded as positive. No advantage is claimed in using horse cells instead of sheep cells. The value of absorption tests was discussed and a new technic described, which the author believes has practical advantages over other methods, although it does not embody any important new principles. Of over 300 samples of normal serum examined by this method, 5 contained small amounts of an antibody indistinguishable from that found in the serum of patients with infectious mononucleosis and 10 others contained a sheep cell agglutinin probably different from any yet recognized in human serum.

Kaufman [221] presents a careful review of the literature and his own observations on the occurrence of false positive serologic reactions for syphilis in patients with infectious mononucleosis. He considers that the actual incidence of recognized false positive reactions in patients with this disease would seem to be between 2 and 10 per cent. It is advised by the author that when a Wassermann reaction is encountered which is suspected of being falsely positive, a heterophile antibody test should

219. Warren, E. W.: Observations on Infectious Mononucleosis, Am. J. M. Sc. **201**:483, 1941.

220. Barrett, A. M.: The Serological Diagnosis of Glandular Fever (Infectious Mononucleosis): A New Technique, J. Hyg. **41**:330, 1941.

221. Kaufman, R. E.: False Positive Serologic Reactions for Syphilis in Infectious Mononucleosis, J. Lab. & Clin Med. **26**:1439, 1941.

be performed. The cause of the false positive reactions in patients with infectious mononucleosis is unknown. Eagle considers that they may be due to the effect of some native amboceptor (antibody for sheep red cells) on the Wassermann reaction. The possibility that this may account for the false positive flocculation tests (Kline, Kahn, Eagle, Meinicke, etc.) is clearly excluded, since red cells are not employed in this type of reaction. The suggestion is made by Kaufman that patients should not be treated for syphilis until serologic reactions suspected of being falsely positive have had a sufficient opportunity to revert to negative.

Mohr, Moore and Eagle [222] call attention to the fact that infectious mononucleosis has been reported repeatedly as a cause for biologic false positive tests for syphilis. In a review of the literature they found that the various serologic tests for syphilis are observed to yield positive reactions in 18 to 50 per cent of cases of infectious mononucleosis. Bernstein is cited as stating that the false positive reaction is transitory, rarely occurs over a longer period than three months and generally reverts to negative before the end of the third week of the disease. According to the authors, the nonspecificity of the tests for syphilis extends to the complement fixation (Wassermann) and the flocculation (Kahn, Kline, Eagle, Hinton and Laughlen) tests. Not included in this statement, however, is the complement fixation test with a spirochetal antigen (the so-called "pallida" test). It is possible that this procedure, like the Kahn verification test, may prove useful in the differentiation of positive serologic reactions due to syphilis and those due to other causes.

King [223] reports the case of a 23 year old consulting engineer who had experienced the symptoms of infectious mononucleosis for two and a half weeks. On the morning of entry into the hospital, he got out of bed to go to the toilet and was seized with a sudden agonizing pain in the abdomen which radiated through to the back. Laparotomy was performed promptly, and the spleen was seen to be ruptured and draining blood freely. Splenectomy was done, and recovery was uneventful. The patient's blood showed the characteristic changes of infectious mononucleosis; the heterophile antibody reaction was positive in a dilution of 1 : 1,256, and the symptoms prior to the acute abdominal episode were clear indications that the patient was suffering from this disease when the spontaneous splenic rupture occurred. The spleen weighed 660 Gm. and presented a microscopic picture which was

222. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions in Tests for Syphilis: II. Occurrence with Organic Diseases Other Than Syphilis, Arch. Int. Med. **68**:1161 (Dec.) 1941.

223. King, R. B.: Spontaneous Rupture of the Spleen in Infectious Mononucleosis: Report of a Case, New England J. Med. **224**:1058, 1941.

reported as compatible with infectious mononucleosis. Aside from a possibly similar occurrence which was recorded in 1932, the literature contains no report suggesting rupture of the spleen in this condition. It is of interest to record that we observed a case in the autumn of 1941 in which it was highly probable that the spleen ruptured after slight trauma in a patient with infectious mononucleosis.

Philip [224] reports the case of a man aged 21 who had fever and pain in the abdomen of five days' duration. Physical examination was of no assistance in disclosing the cause of the patient's symptoms. The blood, however, showed 58 per cent lymphocytes on the initial examination, and later they increased to 66 per cent. This led to a heterophile antibody test, which was reported as yielding a positive reaction in a dilution of 1:256. It was established, therefore, that the patient had infectious mononucleosis and was 1 of the group of almost 20 per cent of the patients with this disease whose chief complaint is abdominal pain. The author suggests that all patients with unexplained fever, especially in the presence of lymphocytosis, should have a heterophile antibody test done despite the absence of lymphadenopathy or splenomegaly.

Martin [225] emphasizes the diagnostic difficulty which may be experienced when jaundice appears in a patient with infectious mononucleosis before lymph glands become enlarged. Under such circumstances, the diagnoses which are likely to be considered are catarrhal jaundice and cholecystitis. The possibility arises that an erroneous diagnosis of the preeruptive stage of syphilis may be made, as the Wassermann reaction may also be positive for patients with infectious mononucleosis. The author reports 2 cases of jaundice associated with infectious mononucleosis. In 1 case the jaundice was prominent and preceded the usual glandular enlargement, while in the other it occurred as a transient feature during the course of an otherwise typical attack of infectious mononucleosis. Martin believes that the jaundice is of the obstructive type and probably arises from enlargement of glands in the hilus of the liver.

Sadusk [226] has considered the importance of the cutaneous eruption and the false positive Wassermann reaction which sometimes occur in cases of infectious mononucleosis. According to him, the changes in the skin may resemble those characteristic of German measles, typhoid fever, syphilis, scarlet fever, serum disease or even typhus fever. The

224. Philip, A. J.: Infectious Mononucleosis: Unusual Case, New York State J. Med. **41**:1664, 1941.

225. Martin, L.: Glandular Fever with Jaundice: Report of Two Cases, Lancet **2**:480, 1941.

226. Sadusk, J. F., Jr.: The Skin Eruption and False Positive Wassermann in Infectious Mononucleosis (Glandular Fever), Internat. Clin. **1**:239, 1941.

occurrence of the cutaneous manifestations of the disease and the false positive Wassermann reaction, either singly or together, has been noted previously, but the association is perhaps not well known. A comprehensive review of the literature relating to the cutaneous manifestations of infectious mononucleosis and the false positive Wassermann reaction is given. The author observes that the rash appears most frequently from the fourth to the tenth day of the disease, although it may be as early as the third and as late as the twentieth day. It usually involves the trunk and the upper portion of the arms and occasionally the face and forearms. Itching is mild or absent, and the rash fades in two to seven days without desquamation except in rare instances after the erythematous type. It is usually stated that the rash is present in 17 to 19 per cent of cases, but in the author's experience it has occurred in only 7 per cent, which is more in accord with Bernstein's figure of 9 per cent. The exanthem is macular or maculopapular, although erythematous, urticarial, petechial, purpuric and vesicular types have been described. It has been known since 1928 that a temporarily positive Wassermann reaction may occur during the course of infectious mononucleosis. According to the literature reviewed, this is probably present in 8 to 16 per cent of cases, depending on the frequency with which the blood is tested. The false positive reaction ordinarily appears during the second week of the disease and usually reverts to negative within two weeks, although occasionally it may persist for over two months and even as long as three months. The false reaction affects the result of the Kahn test (or other types of flocculation procedures) as well as the Wassermann reaction. The nature of any of the immunologic reactions in cases of infectious mononucleosis has not been adequately explained, although several suggestions relating to the cause are made by the author.

Thomsen [227] describes 3 cases of infectious mononucleosis in which combined treatment with sulfanilamide and convalescent serum was employed. The results were gratifying, as evidenced by a rapid return of the body temperature to normal and a disappearance of all symptoms. In comparing 31 cases in which treatment was with sulfanilamide alone with a control group in which no special form of therapy was used, the author concluded that apparently the treatment may shorten the course of the disease somewhat but not sufficiently to justify definite conclusions. According to him, sulfanilamide may exert its beneficial effects on the secondary invading organisms which are responsible for some of the pathologic changes in the mouth and throat rather than on the primary cause of the disease.

227. Thomsen, S.: Effect of Sulfanilamide on Infectious Mononucleosis, Ugesk. f. læger **102**:779, 1940.

LYMPHOMATOID DISEASES, LEUKEMIA AND RELATED DISORDERS

Hodgkin's Disease.—In his analysis of 212 cases of Hodgkin's disease Goldman [228] noted that the disease exacts its toll from all races and afflicts males twice as frequently as females. The incidence was greatest in the third decade of life, although in his series of cases the ages ranged from 6 to 76 years. The initial symptom presented in 79 per cent of the cases was glandular enlargement, whereas in only 8 per cent the patients complained primarily of cachectic symptoms. Unilateral glandular enlargement usually developed first, a differential diagnostic point in Hodgkin's disease, since in leukemia and lymphosarcoma lymphadenopathy is most frequently bilateral. Splenomegaly commonly occurred late in the course of Hodgkin's disease. The skin was involved in 38 per cent of cases, the lesions consisting of exfoliative dermatitis or multiple nodules, with pruritus as an outstanding symptom. In 7 per cent skeletal lesions occurred, which resembled metastatic carcinoma in roentgenologic appearance. In 5 per cent of the cases definite involvement of the nervous system was present, with the spinal cord most commonly affected. The average length of life after the onset of symptoms was thirty-two months. In his analysis of the blood picture the author found that neutrophilia, relative monocytosis and lymphocytopenia were most characteristic, while eosinophilia occurred in only 20 per cent of the cases.

In their analysis of 65 cases of Hodgkin's disease in British patients Baker and Mann [229] found no definite etiologic relation between tuberculosis and Hodgkin's disease and noted no characteristic blood picture. In their patients fever was usually associated with visceral or deep glandular involvement, while the average length of survival after the onset of symptoms was eighteen months. Surgical eradication of involved superficial glands followed by irradiation therapy is advocated if the disease is well localized in an easily accessible region. Otherwise, roentgen therapy must be employed as a palliative measure. Although admitting that surgical intervention has benefited some patients with Hodgkin's disease, O'Brien [230] feels that roentgen rays are still the therapeutic mainstay. He presents a detailed description of his irradiation technic. Sayago [231] notes that radium applied externally to the chest may cause marked shrinkage of deep intrathoracic nodes.

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228. Goldman, L. B.: Hodgkin's Disease: Analysis of Two Hundred and Twelve Cases, J. A. M. A. **114**:1611 (April 27) 1940.

229. Baker, C., and Mann, W. N.: Hodgkin's Disease, Lancet **1**:23, 1940.

230. O'Brien, F. W.: End Results in Irradiated Hodgkin's Disease, Am. J. Roentgenol. **46**:80, 1941.

231. Sayago, C.: Radium Therapy in Hodgkin's Disease, Am. J. Roentgenol. **42**:888, 1939.

Of 54 cases of Hodgkin's granuloma studied by Burger and Lehman,[232] 3 were investigated for the possibility of concurrent brucella infection. In 1 case a culture of the blood was positive for Brucella. They believe the life expectancy of treated patients with Hodgkin's granuloma is three times that of untreated patients. Forbus and Gunter [233] have studied the pathogenicity of strains of Brucella isolated from 5 patients who died of typical Hodgkin's disease. They found that suspensions of tissues from these patients injected into guinea pigs failed to produce typical lesions of brucellosis but that the pure cultures of Brucella melitensis and Brucella suis isolated from these tissues did result in a mild form of the disease when administered intraperitoneally to guinea pigs. Poston and Parsons [234] present their method for the culture of Brucella organisms from lymph nodes.

Acuña and Bonduel [235] report the case of a child with Hodgkin's disease complicated by Mikulicz's syndrome. From a biopsy specimen of a lymph node they isolated a strain of streptococcus to which they attributed etiologic significance, stating that an uncontrolled infection may cause the reticuloendothelial system to react in a pathologic manner producing Hodgkin's disease.

Thoracic lesions are commonly encountered in Hodgkin's disease, according to Vieta and Craver,[236] who diagnosed such lesions in 74 per cent of 335 cases. They believe Hodgkin's disease does not produce a pathognomonic roentgen appearance. Charr and Wascolomis [237] report a case in which hemoptysis was the presenting symptom. At autopsy the right main bronchus was found obstructed by a large polypoid mass of Hodgkin's granuloma. There was also a pleural effusion. The condition of a 15 year old boy was diagnosed by bronchoscopy, according to Hammond,[238] who obtained material for biopsy from a mediastinal mass which had perforated the trachea. Garvin [239] reports the first

232. Burger, R. E., and Lehman, E. P.: Hodgkin's Disease: Review of Fifty-Four Cases, Arch. Surg. **43**:839 (Nov.) 1941.

233. Forbus, W. D., and Gunter, J. U.: Pathogenicity of Strains of Brucella Obtained from Cases of Hodgkin's Disease, South. M. J. **34**:376, 1941.

234. Poston, M. A., and Parsons, P. B.: Isolation of Brucella from Lymph Nodes, J. Infect. Dis. **66**:86, 1940.

235. Acuña, M., and Bonduel, A.: Linfogranulomatosis maligna y sindrome de Mikulicz, Arch. argent. de pediat. **15**:128, 1941.

236. Vieta, J. O., and Craver, L. F.: Intrathoracic Manifestations of Lymphomatoid Diseases, Radiology **37**:138, 1941.

237. Charr, R., and Wascolomis, A.: Pulmonary Lesions in Hodgkin's Disease, J. A. M. A. **116**:2013 (May 3) 1941.

238. Hammond, A. E.: Perforation of the Trachea by Mediastinal Tumor (Hodgkin's Disease), Ann. Otol., Rhin. & Laryng. **50**:929, 1941.

239. Garvin, C. F.: Hodgkin's Diseases of the Heart and Pericardium, J. A. M. A. **117**:1876 (Nov. 29) 1941.

antemortem diagnosis of Hodgkin's disease of the heart and pericardium. By cystoscopy Phillips [240] noted gray-yellow nodules in the bladder of a patient with known Hodgkin's disease in whom dysuria, pyuria and hematuria improved considerably after radiation therapy.

In 2 cases presented by Winkelman and Moore [241] the patients showed evidence of marked lesions of the nervous system. One patient had granulomatous plaques on the dura mater overlying the brain, with associated cerebral softening, and involvement of the spinal cord and the brachial plexus. The other had a commoner type of epidural granuloma compressing the thoracic cord, with resultant symptoms of transverse myelitis. Meyer [242] describes marked improvement following roentgen ray therapy in a case in which vertebral and spinal cord damage was extensive. Lisa [243] reports a case of Hodgkin's disease complicated by herpes zoster and Raynaud's disease.

An interesting type of cutaneous granuloma has been described by Kierland and Montgomery.[244] Erythematous plaques which soon deteriorated into ulcerated areas developed on the chest of an 18 year old youth. Biopsy of nonulcerated plaques revealed histologic changes which were typical of Hodgkin's granuloma.

That the life span may not necessarily be short after the development of symptoms of this dread disease is illustrated by the case reported by Nolan,[245] in which the duration was eight and a half years, and 1 reported by Finkelstein,[246] in which the patient survived fourteen years.

Clinicians have long been interested in the effect of pregnancy on the course of Hodgkin's disease. Kushner [247] and Meyer [242] report that no ill consequences were noted after pregnancies in their patients. The children were apparently normal.

From his experience Steiner [248] concludes that the generally discredited Gordon test is of some value in cases in which the diagnosis of

240. Phillips, R.: Hodgkin's Disease in the Bladder, Lancet **1**:480, 1941.

241. Winkelman, N. W., and Moore, M. T.: Hodgkin's Disease of Central Nervous System: Clinico-Pathological Study, J. Nerv. & Ment. Dis. **93**:82, 1941.

242. Meyer, O. O.: Some Therapeutic Experiences with Hodgkin's Disease, J. A. M. A. **117**:595 (Aug. 23) 1941.

243. Lisa, J. R.: Neurologic Complications in Hodgkin's Disease, New York State J. Med. **40**:62, 1940.

244. Kierland, R. R., and Montgomery, H.: Cutaneous Ulcerative Hodgkin's Disease, Proc. Staff Meet., Mayo Clin. **16**:124, 1941.

245. Nolan: Two Cases of Hodgkin's Disease, New Zealand M. J. **40**:306, 1941.

246. Finkelstein, W.: Unusual Case of Hodgkin's Disease, Connecticut M. J. **5**:687, 1941.

247. Kushner, J. I.: Pregnancy Complicating Hodgkin's Disease (Lymphogranuloma Malignum), Am. J. Obst. & Gynec. **42**:536, 1941.

248. Steiner, P. E.: Reliability and Significance of the Gordon Test in Hodgkin's Disease, Arch. Path. **31**:1 (Jan.) 1941.

Hodgkin's disease cannot be made with certainty from pathologic specimens, although he concurs in the opinion of other recent investigators that the reaction in nonspecific. Of 229 cases of Hodgkin's disease, the reaction was positive in 74 per cent, while in only 2 per cent of 452 control cases were positive results obtained.

Charache [249] reports the presence of Hodgkin's disease in 1 member of a set of homologous twins. The other twin was completely normal.

Lymphosarcoma.—Davis [250] classifies lymphosarcoma of the tonsil into three clinical types. The commonest is that in which one tonsil enlarges rapidly, with involvement of cervical lymph nodes. The tonsil is soft, friable and bleeds easily, and the capsule is absent. The second type is termed anginoid, in which a deep ulcer occurs in the tonsillar region. Lymphadenopathy is usually slight. In the third class there are marked regional lymph node metastases without a prominent primary site. The usual duration of life after the onset of symptoms in any of the three types is less than eighteen months. Wax [251] reports a case in which diagnosis was made by routine pathologic section and emphasizes the importance of such microscopic examination. Garcia Lopez [252] reports a tonsillar lymphosarcoma in a 3 year old boy. The author believes this to be the lowest age recorded for the occurrence of this type of neoplasm. In the case reported by Freedman [253] the hard palate was the primary site, a rare locality for this kind of tumor.

Potzky and Freid [254] state that nasopharyngeal lymphosarcoma rarely erodes the base of the skull to produce a basilar brain syndrome. Nasopharyngeal carcinoma, on the other hand, frequently causes this syndrome. The authors feel that nasopharyngeal lymphosarcoma may be cured by irradiation. They report a case in which skull erosion and symptoms and signs referable to the nervous system did not respond to therapy. At necropsy the bony destruction was found to be due to osteomyelitis rather than to tumor invasion.

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249. Charache, H.: Tumors in One of Homologous Twins: Hodgkin's Disease; Osteogenic Sarcoma, Am. J. Roentgenol. **46**:69, 1941.

250. Davis, E. D. D.: Clinical Aspects of Lymphosarcoma of the Tonsil, Proc. Roy. Soc. Med. **34**:679, 1941.

251. Wax, W. V.: Primary Lymphosarcoma of the Tonsil: Importance of Sending Removed Tonsils to the Laboratory for Pathological Diagnosis, New York State J. Med. **39**:2284, 1939.

252. Garcia Lopez, A.: Linfosarcoma de la amígdala en un niño de 3 años de edad, Bol. Soc. cubana de pediat. **13**:343, 1941.

253. Freedman, L. J.: Primary Lymphosarcoma of the Hard Palate, Am. J. Roentgenol. **43**:702, 1940.

254. Potozky, H., and Freid, J. R.: Osteomyelitis of Occipital Bone Complicating Roentgen Treatment of a Nasopharyngeal Lymphosarcoma, Am. J. Roentgenol. **43**:584, 1940.

Madding and Walters [255] review the clinical and laboratory findings in their series of cases of lymphosarcoma of the stomach. The average age was 47 years, and males were affected six times more frequently than females. The lesion occurred most commonly along the lesser curvature, on the posterior wall or at the pylorus. The duration of symptoms varies from a few months to several years. The typical pain is similar to that of gastric ulcer but is less amenable to medical therapy. The occurrence of an epigastric mass or of gross melena is rare. Achlorhydria or hypochlorhydria is usually present, and examination of the blood commonly reveals a milder anemia than that encountered in cases of gastric carcinoma. Diagnostic roentgen studies may not differentiate lymphosarcoma from carcinoma. The authors believe that radical surgical intervention may effect a cure in the lymphocytoma type but that roentgen ray therapy has only palliative effect. The reticulum cell sarcoma is not favorably influenced by irradiation. Giere [256] reemphasizes the lack of a pathognomonic roentgen appearance of gastric lymphosarcoma, which may have serious consequences, since he feels that prognosis in cases of early stages of the disorder in which treatment consists of surgical intervention and irradiation is better than that in cases of early gastric carcinoma. The author presents his observations in a case in which the diagnosis was based on gastroscopy. Ritter [257] describes a lymphosarcoma which involved two thirds of the stomach. Shulman [258] reports a case of primary lymphosarcoma of the jejunum in which about 4 feet (120 cm.) of intestine was involved. Radical surgical treatment and radiation therapy were instituted, but death ensued five months later from a leakage of the anastomosis. At necropsy no sign of local recurrence was encountered. Schaaf and Kraemer [259] present the first recorded case of lymphosarcoma at the ileocecal valve. The commonest sites for this tumor in the large bowel are the cecum and the rectum, according to Hayes, Burr and Pruit.[260] They describe a case of benign lymphoma of the rectum in which a

255. Madding, G. F., and Walters, W.: Lymphosarcoma of Stomach, Arch. Surg. **40**:120 (Jan.) 1940.

256. Giere, C. N.: Lymphosarcoma, Diagnosed Gastroscopically, J. A. M. A. **117**:173 (July 19) 1941.

257. Ritter, S. A.: Case of Primary Lymphosarcoma Occupying Two-Thirds of the Lumen of the Stomach, Am. J. Surg. **47**:131, 1940.

258. Shulman, S.: Primary Lymphosarcoma of Jejunum, Am. J. Roentgenol. **46**:182, 1941.

259. Schaaf, R. A., and Kraemer, M.: Lymphosarcoma of Ileocecal Valve, Rev. Gastroenterol. **7**:248, 1940.

260. Hayes, H. T.; Burr, H. B., and Pruit, L. T.: Lymphoid Tumors of Colon and Rectum: Report of Case of Simple Lymphoma of the Rectum, Surgery **7**:540, 1940.

confusing diagnostic problem was presented. The difficulty of differentiating rectal lymphosarcoma and rectal carcinoma is emphasized by Lynch and Hamilton.[261] These authors believe that rectal lymphosarcoma arises from the submucosal layer of the bowel wall, with early thickening of and lateral spread through this layer. Later invasion and destruction of the muscular and the subserous layer occur. Adhesions to surrounding structures may then follow, but usually the lines of cleavage are easier to identify than in cases of rectal carcinoma. The relative incidence in the rectum of lymphosarcoma and carcinoma is 1 : 200.

Vieta and Craver [256] describe six types of intrathoracic lesion encountered on roentgen examination of patients with lymphosarcomatous disease. They include: (1) mediastinal involvement; (2) parenchymal infiltration; (3) isolated lesions in the parenchyma of the lung; (4) discrete nodes at the roots of the lung; (5) pleural thickening, and (6) pleural effusion. Of their large series of cases of lymphoblastoma and leukemia, definite intrathoracic pathologic changes occurred in 54 per cent of the cases of lymphosarcoma, 74 per cent of the cases of Hodgkin's disease, 72 per cent of the cases of lymphatic leukemia and 18 per cent of the cases of myelogenous leukemia. They emphasize the extreme variability of the lesions and the lack of a pathognomonic roentgen picture. The authors warn that successful palliation depends on adequate roentgen ray therapy of the widespread, deeper lesions, as well as of those which can be seen or felt. Figoli and Menchaca [262] discuss the symptoms and types of mediastinal tumor, with special emphasis on lymphosarcoma, and Kaufman [263] presents a case of a 3 year old boy with a mediastinal lymphosarcoma, probably of thymic origin.

A case of primary lymphosarcoma of the spleen is reported by Bonney.[264] In spite of surgical removal of the spleen, metastases soon occurred in the liver and spinal cord, with the development of a syndrome of transverse myelitis.

Harrington and Miller [265] present 2 cases of primary lymphosarcoma of the female breast. Since lymphoid tissue does not usually occur in breast tissue, these authors assume a preexisting pathologic change which

261. Lynch, J. M., and Hamilton, G. J.: Lymphosarcoma of the Rectum, Tr. Am. Proct. Soc. **40**:221, 1939.

262. Figoli, C., and Menchaca, F. J.: Sindrome mediastinal por sarcoma linfoblástico (consideraciones acera de los tumores de mediastino), Arch. argent. de pediat. **16**:43, 1941.

263. Kaufman, B.: Lymphosarcoma of Mediastinum Probably of Thymus Origin in a Three Year Old Boy, Arch. Pediat. **57**:274, 1941.

264. Bonney, C. W.: Primary Malignant Tumors of the Spleen with Report of a Case of Lymphosarcoma, J. Lab. & Clin. Med. **26**:630, 1941.

265. Harrington, S. W., and Miller, J. M.: Lymphosarcoma of Mammary Gland, Am. J. Surg. **48**:346, 1940.

results in lymphoid accumulations. Surgical intervention and irradiation are suggested as therapeutic measures.

Gall, Morrison and Scott [266] described the enormous enlargement of the lymph nodes which occurs in the follicular type of malignant lymphoma. Here the normal architecture is replaced by multiple follicle-like nodules; the capsule is involved, and the sinuses are obscured. In a study of 63 cases the authors found that the neoplasm tended to occur in a somewhat older age group than that in which other forms of lymphosarcoma are observed. Retroperitoneal and mesenteric nodes were frequently involved, and splenomegaly occurred in one third of the cases. Hematologic and cutaneous abnormalities were rare.

Combes and Bluefarb [267] have studied 15 cases of giant follicular adenopathy. They feel that the condition is amenable to roentgen ray therapy in its early phase but that the untreated process may develop into lymphosarcoma, Hodgkin's disease or lymphatic leukemia. Baehr and Klemperer [268] describe the onset of this disease as a painless swelling of lymph nodes and spleen without general systemic manifestations. The microscopic pathologic picture of the lymph nodes is described, and the frequency of serous or chylous effusions is emphasized. Late in the disease widespread metastases, including osseous involvement, may occur. This type of tumor is extremely susceptible to irradiation.

The variability of the clinical picture produced by reticuloendothelial neoplasms is described by Budd.[269] This is attributed to the wide distribution of the reticuloendothelial system throughout the body. The lymph nodes may show marked lymphocytic hyperplasia (lymphocytoma), or on the other hand, there may be extensive proliferation of the reticulum cells (reticulum cell sarcoma). When both reticulum cells and lymphocytes are hyperplastic, the disorder may closely resemble Hodgkin's disease. Severe leukocytopenia or frank leukemia may be associated with this type of neoplasm. The reticuloendothelial cells may become differentiated into the monocytic form of leukemia, which may be either of the Schilling or of the Naegeli type. Single or multiple bone lesions are sometimes observed in neoplasms of the reticuloendothelial system.

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266. Gall, E. A.; Morrison, H. R., and Scott, A. T.: Follicular Type of Malignant Lymphoma: Survey of Sixty-Three Cases, Ann. Int. Med. **14**:2073, 1941.

267. Combes, F. C., and Bluefarb, S. M.: Giant Follicular Lymphadenopathy: Association of Giant Follicular Lymphadenopathy and Its Polymorphous Cell Sarcoma Derivative, Symmers' Disease, with Lesions of the Skin, Arch. Dermat. & Syph. **44**:409 (Sept.) 1941.

268. Baehr, G., and Klemperer, P.: Giant Follicle Lymphoblastoma: Benign Variety of Lymphosarcoma, New York State J. Med. **40**:7, 1940.

269. Budd, J. W.: Neoplasms of the Reticulo-Endothelial Tissues, California & West. Med. **55**:84, 1941.

Moore and Weller,[270] in a brief review of the literature, state that most patients with lymphosarcoma die within three years of the onset of the primary symptoms. They usually die within one year after bony lesions are diagnosed. Bony metastases are found exclusively in cases of reticulum cell sarcoma, according to previous surveys. A case of lymphosarcoma is reported in which a four year period of "quiescence," or remission, followed the first course of roentgen ray therapy.

In considering the irradiation therapy of lymphoblastomas, Arons [271] feels that the reticuloendothelial system plays a major role in the resistance of the organism to the spread of the malignant growth. Roentgen ray therapy should aim to protect the cells of this system in order to keep the tumor localized. He advises the use of frequent fractionated doses in order to kill tumor cells already injured by previous roentgen ray treatment. Roberts,[272] on the other hand, feels that large doses of roentgen rays should be employed in an effort to cause local fibrosis and sclerosis of such density that the lymphosarcomatous growth cannot spread.

Progress in experimental studies of lymphomas is evidenced by frequent additions to the literature. During the past year Adamstone [273] has reported the occurrence of reticulum cell sarcoma in chicks following intestinal ulceration induced by a dietary deficiency of vitamin E. The spontaneous appearance of similar tumors has been noted in a colony of rats by Nelson and Morris.[274] Curtis and Dunning [275] are studying a transplantable lymphosarcoma of the mesenteric lymph nodes in rats.

Leukemia. — Kaufmann and Lowenstein [276] have defined acute leukemia as a fatal disease of short duration characterized by the unregulated proliferation of primitive leukocytes in the hemopoietic tissue of the bone marrow, lymph nodes and spleen, with delivery of these cells to the peripheral blood in greater or lesser numbers. Infiltration or metaplasia or both may occur in a wide variety of tissues and organs. In the authors' series of 40 cases the age distribution

270. Moore, C., and Weller, G. L., Jr.: Quiescent Interval and Bone Metastases in Lymphosarcoma, Am. J. Roentgenol. **43**:211, 1940.

271. Arons, I.: Further Studies on Radiotherapy of Lymphoblastoma, Radiology **37**:164, 1941.

272. Roberts, F.: Lymphosarcoma, Brit. J. Radiol. **12**:667, 1939.

273. Adamstone, F. B.: Reticulum Cell Sarcoma Following Ulceration of Intestine in Vitamin E-Deficient Chicks, Arch. Path. **31**:717 (June) 1941.

274. Nelson, A. A., and Morris, H. J.: Reticulum Cell Lymphosarcoma in Rats, Arch. Path. **31**:578 (May) 1941.

275. Curtis, M. R., and Dunning, W. F.: Transplantable Lymphosarcomata of Mesenteric Lymph Nodes of Rats, Am. J. Cancer **40**:299, 1940.

276. Kaufmann, J., and Lowenstein, L.: A Study of the Acute Leukoses, Ann. Int. Med. **14**:903, 1940.

covered the first four decades. In half of their cases the patients at the onset of the disease were 25 or older. This is not in agreement with the usual experience concerning the age incidence of this dyscrasia. Weakness, bleeding tendencies, anorexia, joint pain, fever, sore throat and general malaise were the commonest symptoms. On physical examination, 60 per cent of the patients showed glandular enlargement; 60 per cent, splenomegaly, and about 50 per cent, hepatomegaly. Involvement of the thorax and of bones was frequently noted. The average duration of the disease in this series was ten weeks. In 98 per cent of the cases the patients had anemia at the initial examination, and in 84 per cent there was definite thrombopenia. Roentgen therapy was without benefit in the 9 cases in which it was instituted. The authors express their belief that acute leukemia is due to a maturation abnormality.

Doan and Reinhart [277] found that of their series of 317 cases of leukemia, the disease was myeloid in 33 per cent, lymphocytic in 50 per cent and monocytic in 16 per cent. They were particularly interested in the little understood basophile cell. Cases of myelogenous leukemia with terminal basophilic granulocytosis and primary basophilic leukemia are presented in detail. In a third case both eosinophilic and basophilic granulation within the same cell were noted as a terminal event of myelogenous leukemia. These workers assert that in myelogenous leukemia all three types of granulocytes are hyperplastic but the eosinophils and basophils are more resistant to therapy and may remain elevated in the peripheral blood even during periods of remission.

Beard [278] suggests division of the lymphatic leukemias into two groups —those representing true malignant growths and those representing maturation disturbances. The former group is subdivided into (1) lymphosarcoma, in which little peripheral blood change is noted; (2) leukosarcoma of the Sternberg type, in which sarcoma cells escape into the peripheral blood, and (3) aleukemic leukolymphosarcoma, which occupies a position midway between the two growths just mentioned. The maturation disturbance is described as an arrest similar to that which occurs in pernicious anemia. The abnormal cells then escape into the peripheral blood. The question of an unknown specific deficiency is given attention.

Meyer [279] discusses the pathologic changes in the genitourinary tract associated with leukemia. He states that this tract is involved in 60 to

277. Doan, C. A., and Reinhart, H. L.: Basophil Granulocyte; Basophilcytosis, and Myeloid Leukemia, Basophil and "Mixed Granule" Types: Experimental, Clinical and Pathological Study, with Report of New Syndrome, Am. J. Clin. Path. **11**:1, 1941.

278. Beard, M. F.: Lymphatic Leukemia, Kentucky M. J. **39**:138, 1941.

279. Meyer, L. M.: Pathology of the Genitourinary Tract in Leukemia, Urol. & Cutan. Rev. **45**:693, 1941.

80 per cent of all patients with the disease. The kidneys may show diffuse or nodular infiltration, while masses at the hilus resembling bone marrow may be present. The bladder may present scattered infiltration throughout the wall, and mucosal hemorrhages may be observed cystoscopically.

Pernokis and Freeland [280] have made detailed chemical studies on the blood of 9 patients with myelogenous leukemia and 4 patients with lymphatic leukemia. They found the total lipoids and the fatty acid fractions to be elevated, while the proteins were slightly depressed, with some increase in the globulin fraction. In most instances the values for nonprotein nitrogen, cholesterol, calcium, protein and amino acid were normal.

Lucia [281] in an excellent article has extensively reviewed the therapeutic armamentarium for combating the leukemias. Farrar [282] has likewise contributed a good review of the commoner therapeutic agents. Dowdy and Lawrence [283] stress the need for individualization of therapy. They suggest the use of small doses of roentgen rays (25 to 50 r) and present their technic in detail. They feel that although the life span of the patient is not affected, there is increased comfort during therapy with small doses and a somewhat more rapid convalescence after treatment. Rubenfeld and Scott [284] emphasize once again that as far as treatment is concerned the total white cell count assumes secondary importance with respect to the welfare of the patient. Popp and Watkins [285] call attention to the fact that chronic lymphatic leukemia may enter a phase in which the typical cell is a large or medium-sized lymphocyte (macrolymphocytosis or mesolymphocytosis). These investigators feel that such cell types are extremely sensitive to irradiation and advise cautious use of roentgen ray therapy lest too precipitous a drop in the total white cell count be produced. This "phase" of leukemia is admittedly rather rare. Livingston and Moore [286] have studied a

280. Pernokis, E., and Freeland, M. R.: Blood Chemistry Observations in Leucemias, J. Lab. & Clin. Med. **26**:1310, 1941.

281. Lucia, S. P.: Leukemia: Evaluation of Therapy, California & West. Med. **55**:1191, 1941.

282. Farrar, G. E., Jr.: Chronic Lymphatic Leukemia, Internat. Clin. **1**:78, 1941.

283. Dowdy, A. H., and Lawrence, J. S.: Treatment of Chronic Leukemia by Small Dose Roentgen Ray Technic, J. A. M. A. **116**:2827 (June 28) 1941.

284. Rubenfeld, S., and Scott, L. D.: X-Ray Therapy of Leukemias, Radiology **36**:352, 1941.

285. Popp, W. C., and Watkins, C. H.: Roentgen Therapy for Chronic Macrolymphocytic and Mesolymphocytic Lymphatic Leukemia, Radiology **37**:160, 1941.

286. Livingston, K. F., and Moore, R. D.: Reaction of Leukemic Patients to Sulfapyridine Administration: Preliminary Report, New England J. Med. **223**:975, 1940.

small series of patients with myeloid and with lymphatic leukemia who were treated with sulfapyridine. In 3 cases of lymphatic leukemia they observed a rapid fall of white cell counts within twelve to eighteen hours after the administration of the drug, the effect lasting several days. The decline involved a decrease in the number of lymphocytes, without any evidence of associated neutropenia. The diseased lymph nodes also showed a reaction in the form of further swelling followed by temporary shrinkage. The authors suggest the possibility that roentgen ray therapy might be more efficacious if administered during these periods of local reaction. No similar effect was noted in cases of myeloid leukemia. Considerable interest is being displayed in the use of the radioactive isotope of phosphorus in the therapy of leukemia. Some of the more important studies concerning this agent are summarized in a special section.

It is impossible to include in this review a summary of all case reports which have appeared in the recent literature. Several of unusual interest, however, are mentioned here. Sterne, Schiro and Molle [64] report the case of a patient who died of myelogenous leukemia four and one half years after a diagnosis of pernicious anemia had been made. The patient responded satisfactorily to liver therapy until the leukemia made its appearance. The authors did not attempt to relate the two illnesses, expressing the belief that they were coincidental. Kemp and Williams [287] reported a case of chloroma in which marked involvement of the meninges overlying both the spinal cord and the brain was noted at autopsy. Pyonephrosis superimposed on chronic myelogenous leukemia developed in a patient observed by Humble.[288] After early death autopsy disclosed a heterotopic focus of bone marrow at the renal hilus causing obstruction to urinary outflow. This focus of marrow contained immature red and white cells in various developmental stages as well as megakaryocytes.

The controversy over the origin and the developmental status of the monocyte is reflected in the paper by Hall and Watkins,[289] who report the case of a 23 year old woman who gave a five year history of loss of weight, fever and a mass in the left upper quadrant of the abdomen. Over a three month period of observation following a course of roentgen ray therapy, the blood picture changed from that of typical myelogenous leukemia to that of a monocytic dyscrasia. In this period the monocyte count rose from 0 to 93 per cent. Death occurred nine months later.

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287. Kemp, T. A., and Williams, E. R.: Chloroma, Brit. J. Radiol. **14**:157, 1941.

288. Humble, J. G.: Heterotopic Bone Marrow in the Renal Hilum Causing Pyonephrosis in an Adult with Chronic Myeloid Leukemia, J. Path. & Bact. **53**:147, 1941.

289. Hall, B. E., and Watkins, C. H.: Myelogenous Leukemia Changing to Monocytic Leukemia: Report of Case, Am. J. Clin. Path. **11**:443, 1941.

The authors believe this to be a case of the Naegeli type of monocytic leukemia. Walsh and Medlar [290] report a case of acute myelogenous leukemia, which they had first believed to be of monocytic type. They suggest that many cells termed monocytes may really be small (thrombocytic type) megakaryocytes. White,[291] on the other hand, believes all monocytes are variants of lymphocytes and feels that the criteria used to classify cells as monocytic are not clearcut.

Friedenberg [292] does not share the view that oral surgical operations are contraindicated for patients with myelogenous leukemia and reports 11 instances of such operations performed without sequelae.

Vallino [293] and Acuña and Vallino [294] report cases of leukemia in children in which both parents had positive serologic reactions for syphilis. One of their patients was a 3 month old boy whose skeletal roentgenograms showed definite bony lesions of syphilis. Pallor had been noted at birth, and at 3 months of age the patient presented petechial hemorrhages, splenomegaly and hepatomegaly. The peripheral blood and the bone marrow contained large numbers of immature white cells which were not classifiable. They believe this to be a case of congenital leukemia in the production of which syphilis may have played a leading role. Vallino states that in her experience most leukemia in children occurs in those whose parents are syphilitic. (Observations of any striking coincidence of leukemia and syphilis have not been reported in the United States or Europe.)

The experimental production of leukemia in animals affords an excellent opportunity for increasing the present meager knowledge of this disease and of the malignant growths as a group. Morton and Mider [295] have applied methylcholanthrene and 3,4-benzpyrene to the skin of mice, with subsequent development of leukocytosis (50,000 to 100,000 white cells per cubic millimeter). Ninety per cent of the cells resembled lymphoblasts. These cells appeared in the blood two to four weeks before lymphadenopathy was recognizable. Furth [296] has also produced mouse leukemia by the use of carcinogenic agents and presents

290. Walsh, J. C., and Medlar, E. M.: Acute Myelogenous Leukemia, Am. J. Cancer **40**:447, 1940.

291. White, E.: A Case of Monocytic Leukemia, M. J. Australia **2**:167, 1941.

292. Friedenberg, M.: Myelogenous Leukemia and Its Influence upon Postoperative Healing: Dental Study with Report of One Case, J. Am. Dent. A. **28**:943, 1941.

293. Vallino, M. T.: Leucemia mieloside en un nino de 3 meses, Prensa méd. argent. **28**:194, 1941.

294. Acuña, M., and Vallino, M. T.: Leucemia congénita aguda, Arch. argent. de pediat. **16**:407, 1941.

295. Morton, J. J., and Mider, G. B.: Some Effects of Carcinogenic Agents on Mice Subject to Spontaneous Leukoses, Cancer Research **1**:95, 1941.

296. Furth, J., and Barnes, W. A.: Differences Between Malignant Blood Cells from Induced and Spontaneous Leukemias of Mice, Cancer Research **1**:17, 1941.

data on genetic studies of his strains of mice. Law [297] used 0.5 per cent 9,10-dimethyl-1,2-benzanthracene in his experiments on mice. Of 119 animals, lymphomatosis occurred in 101, while myeloid leukemia developed in 8 and monocytic leukemia in 2. There was a latent period of about three and one-half months before the blood dyscrasias appeared. Young mice were found to be more susceptible than older animals. In 30 per cent of the controls leukemia developed spontaneously. Engelbreth-Holm and Lefèvre [298] have likewise noted acceleration of neoplastic growth by dimethylbenzanthracene. Sturm [299] has been able to produce resistance in host animals (rats) by injection of living embryonic cells from 18 day old (Wistar rat) embryos. Doljanski, Goldhaber and Pikovski [300] in their studies on fowl leukosis have found that the causative agent can be inactivated by adequate doses of roentgen rays.

The depressant action of colchicine on cell mitosis is well established. The maturation arrest usually occurs at the metaphase stage, with resultant production of bizarre forms called "colchicine figures." Paul, Brown and Limarzi [301] state that after administration of colchicine leukocytopenia occurs first, followed by leukocytosis. Because of the mitotic arrest produced by colchicine the drug was given a therapeutic trial in a patient with myelogenous leukemia. Forty-eight milligrams was administered intramuscularly over a period of six weeks. The downhill course of the illness appeared unaffected. At autopsy degeneration of cells in lymphatic tissue, with bizarre nuclear changes, was noted. While these appeared to be characteristic of the colchicine effect, they could not be considered specific for this drug. In the normal tissues no mitotic abnormalities were noted.

In a short article Hamilton-Paterson [302] submits photographic evidence for his statement that mitosis is comparatively common in the bone marrow and in other tissues of persons suffering with monocytic leukemia.

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297. Law, L. W.: Induction of Leukemia in Mice Following Percutaneous Application of 9, 10-Dimethyl-1, 2-Benzanthracene, Cancer Research **1**:564, 1941.

298. Engelbreth-Holm, J., and Lefèvre, H.: Acceleration of Development of Leukemias and Mammary Carcinomas in Mice by 9, 10-Dimethyl-1, 2-Benzanthracene, Cancer Research **1**:102, 1941.

299. Sturm, E.: Induced Resistance to a Transplantable Lymphatic Leukemia in Rats, Cancer Research **1**:627, 1941.

300. Doljanski, L.; Goldhaber, G., and Pikovski, M.: Inactivation of Causative Agent of Fowl Leukosis by X-Rays, Nature, London **147**:481, 1941.

301. Paul, J. T.; Brown, W. O., and Limarzi, L. R.: Effect of Colchicine on Chronic Myeloid Leukemia, Am. J. Clin. Path. **11**:210, 1941.

302. Hamilton-Paterson, J. L.: Mitosis in Monocytic Leukaemia, J. Path. & Bact. **52**:273, 1941.

The leukemoid blood reactions complicating various primary diseases constitute an interesting and often confusing group of blood dyscrasias. Hill and Duncan [303] define a leukemoid state of the peripheral blood as one in which the total white cell count exceeds 50,000 or in which the presence of immature cells is detected. The origin of such a reaction may lie in one of the following processes: (1) bone marrow irritation or stimulation, such as may occur in osteomyelitis, metastatic carcinoma or chronic granuloma or as a reaction to intravenous therapy; (2) liberation leukocytosis, the result of marrow response to overwhelming demand, such as may be associated with acute hemolysis in therapy with sulfanilamide or one of its derivatives, blackwater fever, familial hemolytic anemia, sickle cell anemia, phenylhydrazine therapy, pernicious anemia in crisis and sepsis and also during recovery from granulocytopenia or in impending death from infection, and (3) ectopic hemopoiesis, as in agnogenic myeloid metaplasia. The authors feel that the differential blood count is of definite value in separating leukemoid reactions from true leukemia. In the former disorders, the immature white cells are morphologically normal, myeloblasts usually constitute less than 10 per cent of the total differential count and the numbers of nucleated red cells often bear a direct relation to the degree of white cell immaturity. These conditions generally do not exist in true leukemia. Hadley [304] feels that the leukemoid blood picture results chiefly from a maturation block. Lisa, Solomon and Gordon [305] report a case of leukemoid reaction in the presence of bronchogenic carcinoma with metastases to the bones, liver and spleen. The total white cell count was 28,000, with many immature red cells and white cells, chiefly of the lymphocytic series. Konwaler [306] observed a leukemoid blood reaction in a patient with metastatic melanoma. Over a period of three months the blood picture remained entirely compatible with that of lymphatic leukemia.

Another blood dyscrasia apt to be confused with myelogenous leukemia is that termed by Jackson and his co-workers "agnogenic myeloid metaplasia." Carpenter and Flory [307] list the principal features

303. Hill, J. M., and Duncan, C. N.: Leukemoid Reactions, Am. J. M. Sc. **201**:847, 1941.

304. Hadley, H. G.: Symptomatic Leukemia, Brit. J. Radiol. **14**:113, 1941.

305. Lisa, J. R.; Solomon, C., and Gordon, E.: Leukemoid Reaction in Carcinomatous Skeletal and Splenic Metastases: Case Report, Am. J. Cancer **40**:227, 1940.

306. Konwaler, B. E.: Metastatic Melanoma with Lymphatic Leukemia Blood Picture, Am. J. Clin. Path. **11**:761, 1941.

307. Carpenter, G., and Flory, C. M.: Chronic Non-Leukemic Myelosis: Report of Case with Megakaryocytic Myeloid Splenomegaly, Leukoerythroblastic Anemia, Generalized Osteosclerosis and Myelofibrosis, Arch. Int. Med. **67**:489 (March) 1941.

of the disease as (1) osteosclerosis and fibrosis of the marrow cavities; (2) compensatory myeloid tissue in the spleen and the liver, with resultant splenomegaly, and (3) a blood picture characterized by decrease in the erythrocytes, leukocytes and platelets, together with the presence of small numbers of immature red and white cells and occasional megakaryocytes. They suggest that the condition may be the result of hyperplasia of multipotential mesenchymal tissues due to an unknown stimulus. Jordan and Scott [308] point out that little is known of the mechanism of this disorder and classify patients exhibiting such metaplasia into three etiologic groups: (1) those with certain sclerosing tumors and with chemical poisoning (phosphorus, strontium), (2) those with Albers-Schönberg's disease (*Marmorknochen*) and (3) those with osteosclerosis associated with blood dyscrasias. The authors accept the unitarian view of totipotentiality of the lymphocyte. They suggest that in the presence of gradual consumption of bone marrow by a pathologic process lymphocytes may be stimulated to undergo transformation into specialized blood cells in ectopic foci located in the spleen and lymph nodes. Because of a defective filtration mechanism immature cells escape into the peripheral blood. Hence the metaplasia is compensatory and may overshoot or undershoot the normal blood values in the effort to carry on hemopoiesis. The authors feel that such an explanation would account for the seemingly paradoxic occurrence of polycythemia in a case of atrophy of the bone marrow. Pavlovsky [309] presents a brief account of 9 cases of agnogenic myeloid metaplasia which he has observed. In 1 case the patient died shortly after a course of roentgen ray therapy. In the other 8 the patients were treated conservatively, and all are living. One patient has survived twenty years since the onset of symptoms. Taylor and Smith [310] report the case of a 66 year old man in whom the vertebral, costal and femoral marrow was extensively fibrosed. Ectopic hemopoiesis was encountered at necropsy in the spleen, liver, renal capsules and vestigial remains of hemolymph nodes. No immature red or white cells were noted in the peripheral blood. An excellent review of the prevailing ideas of etiology is appended. Rawson, Parker and Jackson [311] emphasize the possible role of industrial solvents, including benzene and carbon tetrachloride, in the production of myeloid metaplasia. Six patients studied by them gave a history of exposure to such solvents.

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308. Jordan, H. E., and Scott, J. K.: Case of Osteosclerosis with Extensive Extramedullary Hemopoiesis and a Leukemic Blood Reaction, Arch. Path. **32**:895 (Dec.) 1941.

309. Pavlovsky, A.: Metaplasia mieloides compensulare de bazo simulando leucemia mieloides subagudes, Semana méd. **48**:1459, 1941.

310. Taylor, H. E., and Smith, R. P.: Marrow Sclerosis Associated with Massive Myeloid Splenomegaly, Arch. Path. **31**:803 (June) 1941.

311. Rawson, R.; Parker, F., Jr., and Jackson, H., Jr.: Industrial Solvents as Possible Etiologic Agents in Myeloid Metaplasia, Science **93**:541, 1941.

Polycythemia.—Orten [312] presents a brief account of the history of experimental cobalt polycythemia, stating that it was first reported in 1931. In rats there is an increase in the number of erythrocytes but no concomitant leukocytosis. Such experimental polycythemia has also been produced in dogs, rabbits, pigs, mice, guinea pigs and frogs. In sheep and cattle, and possibly in dogs, cobalt may be necessary for normal hemopoiesis. Although the mechanism of the cobalt effect is not yet completely understood, the element is believed to stimulate the marrow tissue directly, since reticulocytosis occurs before increase of the erythrocyte count. Cobalt may act in some way to interfere with cell respiration and thus call forth a compensatory polycythemia. There is no evidence to support the theory that this type of erythrocytosis develops as a result of decreased blood destruction.

Davis [313] has observed that the increase of blood volume in animals with cobalt polycythemia results primarily from an augmented red cell mass. This author [314] has also found that administration of raw liver or of choline to dogs with cobalt polycythemia depresses the excessive hemopoiesis, as measured by decrease of the reticulocyte count to normal. Hepatic choline is probably responsible for the effect of liver in these experiments. Choline acts in a "muscarine-like" manner, causing better oxygenation of the bone marrow by means of vasodilatation. Another vasodilator, sodium nitrite, likewise caused depression of the excessive blood formation. Decrease in both plasma and cell volume occurred proportionally so that any diluent effect has been ruled out. Conversely, Davis [315] investigated the effects of vasoconstrictor drugs on the erythrocyte count and the hemoglobin level and found that in normal dogs and rabbits a significant rise of the red cell count occurred after administration of ephedrine. In polycythemic rabbits a further increase in the erythrocyte level was observed. In order to exclude increases of circulating erythrocytes attendant on the splenic constriction produced by vasopressor drugs, animals were splenectomized and found to react to ephedrine in a manner similar to that of subjects not operated on. The administration of amphetamine also increased the erythrocyte count consistently in normal dogs but unpredictably in normal rabbits. When-

312. Orten, J. M.: Experimental Polycythemia, Detroit M. News, Educ. Issue **32**:42, 1941.

313. Davis, J. E.: Blood Volume in Cobalt Polycythemia, Proc. Soc. Exper. Biol. & Med. **45**:671, 1940.

314. Davis, J. E.: Mechanism of the Depressant Action of Liver and Choline Hydrochloride upon Experimental Polycythemia: Effect of Sodium Nitrate and Choline Derivatives on Polycythemic Dogs, J. Pharmacol. & Exper. Therap. **70**:408, 1940.

315. Davis, J. E.: Production of Experimental Polycythemia in Dogs, Rabbits and Man by Daily Administration of Ephedrine; and by Amphetamine in Dogs, Am. J. Physiol. **134**:219, 1941.

ever rises of the hemoglobin level and the red cell count occurred, an increase in reticulocytes was first noted. The effects produced by these vasoconstrictor drugs were only temporary. The blood returned to the preexperimental level seven to ten days after their discontinuance. In a human subject whose blood values were normal, administration of ephedrine caused a rise of 800,000 erythrocytes per cubic millimeter and an elevation of hemoglobin concentration of 11 per cent over a two week period. The leukocytes were not affected. Davis believes that the pressor drugs reduce the blood flow through the bone marrow, with resultant hypoxemia and stimulation of erythropoiesis. Frost, Spitzer, Elvehjehm and Hart [116] have noted an inhibition of the hemopoietic effect of iron and copper in anemic animals to which cobalt had been previously fed. Active hemopoiesis was resumed after administration of liver. In their studies of the circulatory adjustments in human beings with polycythemia, Stewart, Wheeler and Crane [316] have observed decrease of the cardiac volume output and increase of the arteriovenous oxygen differential. Both of these variations were proportional to the increase in hemoglobin and in erythrocytes. After effective therapy the values for cardiac volume output and arteriovenous oxygen differential returned to normal. These investigators found the cardiothoracic ratio to be normal in 5 of their 6 patients, while in 1 patient it showed a slight increase. They suggest that the increased viscosity of the blood causes slowing of the circulation, with subsequent increase of the arteriovenous oxygen differential. The relatively slow return of the blood to the heart decreases cardiac output, an effect which is not especially detrimental, since the increased blood hemoglobin of polycythemic patients makes a larger cardiac output unnecessary for the maintenance of adequate fixed tissue oxygenation.

Erickson and her associates [317] have analyzed the chemical composition of the red cell in a small series of polycythemic patients (2 with polycythaemia rubra vera and 1 with polycythemia secondary to a cardiac lesion). In those with primary polycythemia the hemoglobin and the nonhemoglobin protein fraction of the erythrocytes was lower than normal, whereas in the patient with compensatory erythrocytosis these values were within normal limits. The content of total lipids, cholesterol and phospholipids in the red cells was elevated in both types of polycythemia. The composition of the erythrocyte stroma in the red cells of these patients differed from that in red cells of beef embryos in which physiologic erythrocytosis is present.

316. Stewart, H. J.; Wheeler, C. H., and Crane, N. F.: Circulatory Adjustments in Polycythemia Vera, Am. Heart J. **21**:511, 1941.

317. Erickson, B. N., and others: Correlated Hematologic, Physical and Chemical Studies of Blood and Stroma in Polycythemia and Beef Embryo, J. Lab. & Clin. Med. **26**:1492, 1941.

Hodes and Griffith [318] present a preliminary report of the differential roentgen findings in the chest in 11 cases of primary and 3 cases of secondary polycythemia. In polycythaemia rubra vera increased truncal shadows and increased markings were seen in the middle and peripheral pulmonary fields, explicable on the basis of pulmonic vascular engorgement. In 3 cases the patients also showed sharply circumscribed lesions in the middle pulmonary zone which had remained unchanged for years. In the secondary type of polycythemia there is absence of change in the truncal shadows and in the middle and peripheral pulmonary zones until congestive failure occurs. Prominence of the hilar shadows and the pulmonic conus and right-sided cardiac hypertrophy may be present in the secondary type of polycythemia as additional differential diagnostic aids.

Holbrook [319] has observed the effects of venesection on 10 polycythemic patients. He states that the decrease in hemoglobin level and red cell count is usually discernible within a few days after venesection but that the full effect may not be realized for five to seven weeks. No reticulocytosis follows venesection. The blood volume changes slightly, although the hematocrit reading decreases approximately 4.5 per cent after withdrawal of 400 cc. The symptomatic benefit of a single venesection may last from a few days to one year, with an average duration of two months.

Stover and Herrell [320] report a case of polycythaemia rubra vera in which there developed thrombosis associated with thrombophlebitis of the right subclavian and the right axillary vein. They believe such extensive thrombophlebitis of the upper extremity is rarely encountered. The treatment of this patient consisted of daily venesection for a short period followed by administration of phenylhydrazine in doses of 0.3 Gm. one day each week.

The recent studies of the use of radioactive phosphorus in the treatment of polycythemia are discussed in the following section.

Radioactive Phosphorus.—Since the advent of the cyclotron investigators have had access to radioactive isotopes of several elements which can be used either as "tracers" in the study of the metabolism of these elements or as therapeutic agents. Radioactive phosphorus (isotope P-32) is being extensively used in various types of investigation.

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318. Hodes, P. J., and Griffith, J. Q.: Chest Roentgenograms in Polycythemia Vera and Polycythemia Secondary to Pulmonary Arteriolosclerosis, Am. J. Roentgenol. **46**:52, 1941.

319. Holbrook, A. A.: Use of Venesection in Treatment of Erythremia, Wisconsin M. J. **40**:899, 1941.

320. Stover, L., and Herrell, W. E.: Extensive Thrombosis of Right Subclavian and Axillary Veins Associated with Thrombophlebitis, Lymphedema and Polycythemia Vera, Proc. Staff Meet., Mayo Clin. **15**:817, 1940.

A number of investigators have been studying several phases of phosphorus metabolism with the aid of this isotope, but most of the data concerning the relation of phosphorus to blood dyscrasias have been reported by the group working at the University of California at Berkeley in conjunction with the physicist E. Lawrence. These investigators have studied the effects both of small "tracer" doses of the isotope and of larger therapeutic doses.

To young healthy monkeys [321] single doses of radioactive phosphorus were administered, and the effect on the peripheral blood was noted. The lymphocytes were affected first, a gradual fall being observed a few days after the administration of the agent. The lymphocyte count reached its minimum value after fourteen to twenty days, whereas the granulocytes decreased after between twenty-one and twenty-eight days, and the erythrocytes between thirty-eight and forty-five days. The lethal dose for monkeys was found to be 1.04 millicuries and that for healthy mice 1.37 millicuries per pound of body weight. These quantities represented about ten times the usual therapeutic dose for human beings. Healthy dogs [322] were fed radioactive phosphorus enclosed in rubber so that effects of irradiation of the gastrointestinal lymph tissue might be studied without complicating factors due to absorption of the radioactive substance. It was found that mild lymphocytopenia developed, which might be construed as supportive evidence for the view that the majority of blood lymphocytes originate in the lymph tissues of the gastrointestinal tract.

Comparative studies [323] on the absorption and distribution of radioactive phosphorus in the blood were performed on the blood of normal and of leukemic human subjects. The results indicated that a greater amount of radioactive phosphorus is retained by leukemic than by normal whole blood. The radioactive phosphorus content of plasma reaches a maximum before the second hour after oral administration. It then tapers off to zero on the eighth day. The highest values in the red cells occur between six and twenty-four hours after ingestion and then gradually decline. During the first forty-eight hours after oral administration the content of radioactive phosphorus in the white cells of leukemic patients rises more rapidly to higher levels than is observed in the leukocytes of normal persons. After this early rapid rise the content

321. Scott, K. G., and Lawrence, J. H.: Effect of Radio-Phosphorus on Blood of Monkeys, Proc. Soc. Exper. Biol. & Med. **48**:155, 1941.

322. Erf, L. A.: Note on the Effect of Dermal and Enteral Irradiation by Radio-Phosphorus on the Blood Levels of Dogs, Am. J. M. Sc. **202**:650, 1941.

323. Erf, L. A., and Lawrence, J. H.: Clinical Studies with the Aid of Radioactive Phosphorus: I. Absorption and Distribution of Radio-Phosphorus in the Blood and Its Excretion by Normal Individuals and Patients with Leukemia. J. Clin. Investigation **20**:567, 1941.

of the isotope continues as a high plateau in the white cells of leukemic patients and a lower plateau in the white cells of healthy persons. This difference may be explained by the more rapid reproduction of white cells or by the elevated phosphorus metabolism of white cells in persons with leukemia. After intravenous administration of the isotope the leukocytes in patients with leukemia retained still larger amounts, whereas in normal subjects the concentration of leukocytes was only slightly greater than when the material was given by the oral route.

Excretion data indicate that 25 to 50 per cent of ingested radioactive phosphorus is eliminated by normal persons during a six day period. After the lapse of forty-eight hours a larger amount is found in the urine than in the feces. Persons with leukemia excreted in a similar period between 5 and 25 per cent, of which the larger part consistently appeared in the feces.

In an investigation of the effects of radioactive phosphorus on patients with polycythemia [324] it was noted that the isotope gradually became incorporated into the phospholipid fraction of the red cells. In the blood plasma the ingested isotope rapidly appeared in the phospholipid fraction and reached a maximum concentration in this fraction between the forty-eighth and the ninety-sixth hour after ingestion, whereas the content of radioactive phosphorus in the acid-soluble fraction rose to a maximum even earlier.

In autopsy specimens obtained from patients who died of lymphatic leukemia and who had been treated with radioactive phosphorus, the highest content of the isotope was found in the liver, ribs, vertebral bodies, sternum, spleen, lymph nodes, testes and kidneys.[325]

Previous animal experiments by these investigators at the University of California at Berkeley showed that phosphorus metabolism was markedly altered in leukemic mice. The absorption and retention of radioactive phosphorus was increased. Recently they have studied the phospholipid, the acid-soluble and the nucleoprotein fraction of various tissues and organs, including lymphoma tissue itself.[326] By killing con-

324. Erf, L. A., and Lawrence, J. H.: Clinical Studies with Aid of Radio-Phosphorus: Absorption and Distribution of Radio-Phosphorus in the Blood of, Its Excretion by, and Its Therapeutic Effect on, Patients with Polycythemia, Ann. Int. Med. **15**:276, 1941.

325. Erf, L. A., and Friedlander, G.: Phosphorus Exchange in Tissues of Patients with Lymphoid Leukemia, Proc. Soc. Exper. Biol. & Med. **47**:134, 1941. Erf, L. A.: Retention of Radiophosphorus in Whole and Aliquot Portions of Tissues of Patients Dead of Leukemia, ibid. **47**:287, 1941.

326. Tuttle, L. W.; Erf, L. A., and Lawrence, J. H.: Studies on Neoplasms with the Aid of Radioactive Phosphorus: II. Phosphorus Metabolism of Nucleoprotein, Phospholipid and Acid Soluble Fractions of Normal and Leukemic Mice, J. Clin. Investigation **20**:57, 1941.

trol and leukemic mice at various intervals after administering "tagged" phosphorus, differences in metabolism of radioactive phosphorus in the two groups of mice could be studied. The control group retained 25 per cent of the administered isotope at the end of seven days, whereas 40 per cent was found in the leukemic mice. Leukemic mice showed increased absorption and retention of radioactive phosphorus by nucleoprotein and acid-soluble fractions in the liver, the spleen and the lymph nodes. The phospholipid metabolism is affected only slightly by the presence of leukemic infiltration. In the lymphoma tissue itself there was rapid incorporation of radioactive phosphorus into nucleophosphate, which is probably related to carbohydrate metabolism in the tumor.

The group working at Berkeley feel that radioactive phosphorus is an effective therapeutic agent in the treatment of leukemia and polycythemia.[327] It is simple to administer, and there are no untoward after-effects of irradiation if frequent, small doses (2 millicuries) are used. They have found radioactive phosphorus to be as effective as roentgen rays in the management of patients with chronic leukemia but just as disappointing in the treatment of those with acute forms of the disease. In patients with polycythemia [324] the response is not so rapid as in ones with leukemia. In 3 patients fairly large doses were required to reduce the hemoglobin content and red cell count. The response became manifest about one hundred days after initiating therapy.

Myeloma.—Although osteolytic lesions without generalized osteoporosis are not pathognomonic of multiple myeloma, they are characteristic of the roentgen appearance of the disease, according to Kinney.[328] Metastatic carcinoma and syphilitic lesions of bone give osteoblastic reactions roentgenologically, while generalized osteoporosis is often encountered in hyperparathyroidism. Bence-Jones proteinuria occurs in 50 to 65 per cent of cases of myeloma, and there is evidence of renal damage in 70 per cent. Hyperproteinemia occurs in about half of the cases of multiple myeloma.

Paul and Pohle [329] differentiate solitary bone myelomas into two groups, those which remain localized and those which metastasize, producing the lesions of multiple myeloma. They have reviewed 45 cases of solitary myeloma and find that the dorsal portion of the spine, the pelvis and the femur are the three commonest sites of origin. Males are

327. Erf, L. A.; Tuttle, L. W., and Lawrence, J. H.: Clinical Studies with the Aid of Radio-Phosphorus: IV. Retention in Blood, Excretion and Therapeutic Effect of Radiophosphorus on Patients with Leukemia, Ann. Int. Med. **15**:487, 1941.

328. Kinney, L. C.: Multiple Myeloma, Radiology **35**:667, 1940.

329. Paul, L. W., and Pohle, E. A.: Solitary Myeloma of Bone: Review of Roentgenological Features, with Report of Four Additional Cases, Radiology **35**:651, 1940.

afflicted three times as frequently as females, and the greatest incidence occurs in the fifth decade of life. The differential roentgen diagnosis of the disease is discussed at length. These authors believe that whenever possible a combination of surgical intervention and roentgen irradiation is the most effective therapy.

Several interesting cases have been reported in the literature during the past year. Kirsch [330] described a patient with solitary myeloma who survived for twelve years. Gilmore [331] encountered laryngeal metastasis in a case of multiple myeloma. Unilateral exophthalmos and dural lesions of the spinal cord were noted by Flynn and Sailer.[332] Absence of Bence-Jones proteinuria throughout the course of illness in a patient with multiple myeloma is reported by Berger and Goodman.[333] They noted some transient clinical improvement after roentgen ray therapy. Bertrand, Fuks and Bonadeo Ayrolo [334] reviewed the pediatric literature and found only 12 cases of multiple myeloma reported in children, to which they added an instance of the disease in an 8 year old boy.

BONE MARROW

Study of the bone marrow is assuming an ever increasing importance in the evaluation of blood dyscrasias. In addition, the marrow promises to become an important site for the administration of fluids and drugs in circumstances in which the use of other parenteral routes is not feasible. Tocantins and O'Neill [335] have found the bone marrow to be a suitable pathway for introducing solutions into the general circulation. They report that fifty-two infusions of blood and other materials were administered by them without untoward effects. The quantities varied from 50 to 2,000 cc. and were given by gravity at the rate of 0.4 to 25 cc. a minute. Fluids so introduced leave the medullary space promptly through the emissary veins. In another article Tocantins, O'Neill and Price [336] report the successful use of the intrasternal route for admin-

330. Kirsch, I. E.: Plasma-Cell Myeloma of Bone, of Over Twelve Years' Duration, M. Bull. Vet. Admin. **18**:96, 1941.

331. Gilmore, G. B.: Multiple Myeloma with Laryngeal Metastasis, Arch. Otolaryng. **34**:453 (Sept.) 1941.

332. Flynn, J. E., and Sailer, S.: Unilateral Exophthalmos and Spinal Cord Compression in a Case of Multiple Myeloma, Ohio State M. J. **37**:771, 1941.

333. Berger, S. S., and Goodman, J. I.: Multiple Myeloma: Report of Case, Ohio State M. J. **37**:1163, 1941.

334. Bertrand, J. C.; Fuks, D., and Bonadeo Ayrolo, A.: Mielomas múltiples en un niño de 8 años, Arch. argent. de pediat. **16**:147, 1941.

335. Tocantins, L. M., and O'Neill, J. F.: Infusions of Blood and Other Fluids into the General Circulation via the Bone Marrow: Technique and Results, Surg., Gynec. & Obst. **73**:281, 1941.

336. Tocantins, L. M.; O'Neill, J. F., and Price, A. H.: Infusions of Blood and Other Fluids via the Bone Marrow in Traumatic Shock and Other Forms of Peripheral Circulatory Failure, Ann. Surg. **114**:1085, 1941.

istration of fluid to 72 patients with peripheral circulatory collapse. In a third article Tocantins, O'Neill and Jones [337] present results of intramedullary injections into animals. The application of their technic to problems of pediatric therapy is given considerable attention. Macht [338] has observed prompt absorption of the aqueous solutions of several common drugs after injection into the bone marrow of animals. Drugs in oily vehicles were also well absorbed, although at a somewhat slower rate.

Hebbel [339] describes his technic for obtaining and preparing sternal marrow, using heparin as an anticoagulant. He centrifuges the aspirated mixture of blood and marrow and prepares films of the buffy layer. He estimates that the normal erythrocyte-myelocyte ratio varies from 1 : 1 to 1 : 3.75. The typical bone marrow findings in various blood dyscrasias, such as pernicious anemia, hemolytic anemia, aplastic anemia, agranulocytosis, purpura and leukemia, are well reviewed. Smith [340] discusses the value of marrow studies in diseases of infancy and of childhood. He believes that examination of the sternal marrow during therapy with sulfanilamide or its derivatives is of value in the early recognition of toxic blood reactions. Nucleated cell counts of the sternal marrow below 100,000 per cubic millimeter indicate danger of continued drug administration, and significant decrease of the more mature marrow elements may also give warning of impending reactions. The author discusses the appearance of the bone marrow punctate in the various types of purpura and in hereditary pseudohemophilia, Gaucher's disease, Niemann-Pick disease and Cooley's anemia.

Israels [341] points out that hemoglobin does not normally appear in the developing red cell until it has reached the late normoblast stage, at which time the nucleus has become pyknotic and the cell has lost its powers of reproduction. In pernicious anemia, on the other hand, hemoglobinization occurs at a much earlier stage of red cell development, appearing before the cell has lost its reproductive potentiality. This type of red cell formation is called megaloblastic erythropoiesis as opposed to the normal, or normoblastic, erythropoiesis. Israels also believes that there may be abnormally early hemoglobinization of the normoblast when

337. Tocantins, L. M.; O'Neill, J. F., and Jones, H. W.: Infusions of Blood and Other Fluids via Bone Marrow: Application in Pediatrics, J. A. M. A. **117:** 1229 (Oct. 11) 1941.

338. Macht, D. I.: Absorption of Drugs Through Bone Marrow, Proc. Soc. Exper. Biol. & Med. **47:**299, 1941.

339. Hebbel, R.: Bone Marrow Biopsy, Minnesota Med. **24:**442, 1941.

340. Smith, C.: Recent Advances in the Diagnosis and Treatment of Blood Disorders in Infancy and Childhood, M. Clin. North America **25:**659, 1941.

341. Israels, M. C. G.: Haemoglobinisation of Erythroblasts, J. Path. & Bact. **52:**361, 1941.

there is a sudden demand for erythrocyte production, such as happens in hemolytic anemias. Therefore, early hemoglobinization alone cannot be used in the differentiation of normoblastic and megaloblastic erythropoiesis. He [4] classifies pathologic erythropoiesis into four main types: (1) hyperplastic erythropoiesis with failure of normal proerythroblast maturation (liver deficiency anemia type); (2) hyperplastic erythropoiesis with failure of normoblast maturation (iron deficiency anemia type); (3) hyperplastic erythropoiesis with normal maturation (hemolytic anemia type), and (4) general failure of red cell formation (aplastic anemia type). Most anemias will fall into one of these four categories. Schwind [342] maintains that the argument concerning the occurrence of megaloblasts in normal bone marrow has arisen because of the difficulty of differentiating megaloblasts from normoblasts by the supravital staining methods and concludes that dried, stained films are superior for examining the bone marrow in hyperchromic macrocytic anemias.

Castrodale and his associates [343] have noted hyperplasia of the bone marrow, especially of the myeloid series, after administration of large doses of diethylstilbestrol and estradiol to dogs. The hyperplasia was followed by a phase of hypoplasia. Megakaryocytes were reduced in numbers and appeared shrunken. These changes coincided with the appearance of hemorrhagic tendencies in the experimental animals. The amounts of diethylstilbestrol used were one hundred times greater than the ordinary therapeutic dose.

Blumenthal [344] has found that when homoisotransplants of various mouse tumors grow to a large size the animals may become debilitated and anemic and may display hyperplasia both of erythrocyte and of granulocyte elements in the bone marrow.

Other articles dealing with the role of marrow in hemopoiesis and the changes produced by disease are considered under the appropriate section headings of this review.

SPLENIC DISORDERS

Banti's Syndrome.—Whipple and associates [345] have continued their studies of the internal circulation of the spleen in relation to splenomegaly.

342. Schwind, J. L.: Study of Megaloblast Problem with Supravital Method, Anat. Rec. **78** (supp. 2):55, 1941.

343. Castrodale, D.; Bierbaum, O.; Helwig, E. B., and MacBryde, C. M.: Comparative Studies of the Effects of Estradiol and Stilbestrol upon the Blood, Liver, and Bone Marrow, Endocrinology **29**:363, 1941.

344. Blumenthal, H. T.: Effects of Spontaneous and Transplanted Rat and Mouse Tumors on Red and White Cells in Circulating Blood and Bone Marrow, Cancer Research **1**:196, 1941.

345. Whipple, A. O.: Recent Studies in Circulation of Portal Bed and of the Spleen in Relation to Splenomegaly (Thomas Dent Mütler Lecture), Tr. & Stud., Coll. Physicians, Philadelphia **8**:203, 1941.

It is their contention, based on microscopic study of living mammalian spleens, that the splenic pulp spaces provide the only circulatory link between the arterial and the venous system. Within the pulp spaces, blood is stored, filtered and phagocytosed and the red cells are subjected to hemolytic action.

In a discussion of Banti's syndrome the author maintains that the clinical and pathologic course of the disease is a result of mechanical circulatory obstruction within the portal venous bed leading to engorgement of the spleen and splenomegaly. Studies of the pressure of the blood within the splenic vein made at the time of splenectomy showed increases of two to five times that of the peripheral venous pressure. Such obstruction may be intrahepatic or extrahepatic. The intrahepatic type may be caused by Laennec's cirrhosis, by cardiac decompensation with periportal scarring or by blocking of portal vein radicles by parasites. Extrahepatic obstruction may result from traumatic or inflammatory scarring involving the portal bed. In children congenital stenosis of the splenic vein has been encountered. In cases of splenomegaly due to extrahepatic obstruction, cirrhosis of the liver will not develop after splenectomy if a normal liver is present at the time of operation. The occurrence of hematemesis subsequent to the removal of the spleen depends on the site of the obstruction of the portal bed which caused the splenomegaly. Only in cases of disorders affecting the splenic vein will subsequent prevention of hematemesis result; in other types of extrahepatic, and in intrahepatic, obstruction portal hypertension will eventually ensue. The histopathologic picture of spleens removed from patients with "portal hypertension" includes, characteristically, widening and distention of veins, with resultant compression of the pulp spaces, and fibrosis at the periphery of the follicles due to hemorrhages from back pressure as the blood passes from the arterial capillaries into the pulp.

Pregnancy complicating splenic anemia has been reviewed by Robins,[346] who found only 12 cases reported in the literature between 1918 and 1940. Three cases, of which 1 was fatal, of hemorrhages from the cervix during the postpartum period were noted. Five patients underwent splenectomy during pregnancy, and in 2 instances both mother and child died at delivery or soon thereafter.

The results of splenectomy in patients with Banti's syndrome are given by Wada.[347] Of a series of 17 patients, the operative mortality was highest in those with advanced hepatic damage. Several patients,

346. Robins, S.: Splenic Anemia Complicating Pregnancy: Review of Literature and Case Report, Virginia M. Monthly **68**:86, 1941.

347. Wada, S.: Remote Postoperative Results in Thirty-Three Cases of Splenectomy, Okayama-Igakkai-Zasshi **53**:1711, 1941.

despite severe impairment of hepatic function, lived more than three years after splenectomy. Otuka [348] feels that splenectomy is justified by the increase in life expectancy. Of 24 patients who survived the postoperative period, 5 lived more than ten years. Splenectomy should be done early to prevent subsequent hepatic damage, according to this author. Cruz [349] feels that splenectomy is indicated if dangerous hemorrhage exists, even in the presence of ascites and hepatic damage. The best results, however, may be expected if the liver is unimpaired. Haden [350] believes the operation should be done in cases of portal congestion and bleeding varices and in the face of evidence of bone marrow depression. He reports that only 2 of 9 patients with preoperative gastrointestinal bleeding who survived operation for one year or more remained permanently free from hemorrhage. The author followed up 21 patients after splenectomy. Six patients died as an immediate result of the operation; 2 died in less than one year, 1 from pulmonary embolism and 1 from cerebral hemorrhage, and 4 suffered fatal gastrointestinal hemorrhages occurring five to seven years after splenectomy. Six other patients survived in good health for one to ten years after operation. Haden also considers splenectomy of value in certain cases of cirrhosis of the liver associated with splenomegaly.

The hematologic changes following splenectomy were carefully studied in 19 patients by Singer, Miller and Dameshek.[351] These include the presence of Howell-Jolly bodies and target cells in the peripheral blood. Many of the red cells are abnormally thin, which accounts for their increased resistance to hypotonic solution of sodium chloride. Fecal output of urobilinogen was decreased, and the lysolecithin content of the peripheral blood was low. The authors describe a "hyposplenic state" characterized by the findings just mentioned which occurs in patients with atrophy of the spleen and contrast this condition with the "hypersplenic state" associated with leukocytopenia, thrombopenia and increased fragility of red cells. The possibility in these two conditions of a reciprocal relation of the spleen and the bone marrow is pointed out.

Gaucher's Disease.—The results of splenectomy performed during the course of Gaucher's disease are reviewed by Logan,[352] who discusses

348. Otuka, T.: Resultate der Splenektomie bei der sogenannten Banti'schen Krankheit, Zentralbl. f. Chir. **68**:307, 1941.

349. Cruz, R.: Anemia esplénica o enfermedad de Banti, Rev. méd. de Chile **69**:303, 1941.

350. Haden, R. L.: Selection of Cases for Splenectomy, Illinois M. J. **79**:421, 1941.

351. Singer, K.; Miller, G. B., and Dameshek, W.: Hematologic Changes Following Splenectomy in Man, with Particular Reference to Target Cells, Hemolytic Index and Lysolecithin, Am. J. M. Sc. **202**:171, 1941.

352. Logan, V. W.: Results of Splenectomy in Gaucher's Disease, Surg., Gynec. & Obst. **72**:807, 1941.

1 case of his own and 7 others previously reported. He concludes that the operation is justified by the observed results. He noted striking clinical improvement, including cessation of hemorrhage, decreased size of the liver, lessened cutaneous pigmentation and gain in body weight. The preoperative leukocytopenia was replaced by persistent leukocytosis. A decreased incidence of infections of the upper respiratory tract was observed, and there were no deaths from acute intercurrent pulmonary infections. The mortality rate from splenectomy was about 15 per cent.

Christianson [353] administered pure cerebrosides intraperitoneally to rabbits and after an interval observed lipid deposits in the liver, spleen and lymph nodes similar to but less extensive than those encountered in cases of Gaucher's disease.

Niemann-Pick Disease.—Niemann-Pick disease is reviewed by Maurer,[354] who compiled 58 cases reported in the literature since 1914, when the syndrome was first described. The high incidence of the disease in members of the Jewish race, its insidious onset in early life and its fatal termination within two and one-half years are emphasized. The blood findings include anemia and leukocytosis, vacuolization of lymphocytes and high plasma contents of cholesterol, lipid phosphorus and fatty acids. Splenomegaly and hepatomegaly are consistently present. No successful therapeutic measure is known, and splenectomy and irradiation with radium are of little value. The author observed 4 cases and reports the necropsy observations in 3.

HEMORRHAGIC DISORDERS AND BLOOD COAGULATION

General Observations.—The hemorrhagic diatheses are classified as to causation by Haden and Schneider.[355] In 74 of 310 cases of abnormal bleeding, purpura was observed without a deficiency of platelets. In these cases an increased capillary permeability is suggested by the authors as the important factor in abnormal bleeding. Allergy, rheumatic disease and renal disease were the most common causes of nonthrombopenic purpura in this group. Abnormal blood coagulation is given by the authors as an additional important factor in the causation of hemorrhagic diatheses.

Perlman and Fox [356] analyzed 355 cases in which anatomic evidence of hemorrhagic diathesis was encountered at necropsy, an incidence of

353. Christianson, O. O.: Experimental Lesions Produced by Cerebrosides, Arch. Path. **32**:369 (Sept.) 1941.

354. Maurer, L. E.: Niemann-Pick's Disease: Report of Four Cases, Rocky Mountain M. J. **38**:460, 1941.

355. Haden, R. L., and Schneider, R. W.: The Hemorrhagic Diathesis: Review of Three Hundred and Ten Cases, Am. J. Clin. Path. **11**:263, 1941.

356. Perlman, L., and Fox, T. A.: Hemorrhagic Diathesis: Analysis of Three Hundred and Fifty-Five Autopsy Reports, Arch. Int. Med. **68**:112 (July) 1941.

3.4 per cent in the 10,355 autopsy records studied. These authors classified the cases into 4 groups according to the cause of the hemorrhagic diathesis: (1) platelet deficiencies, 22 per cent; (2) abnormalities of the capillary walls, 66 per cent; (3) abnormalities of the clotting elements of the blood, 10 per cent, and (4) miscellaneous causes, 2 per cent. An altered capillary permeability occurred with infectious states in 50 per cent of all cases studied in which there was a hemorrhagic diathesis. Among the infectious conditions, bacterial endocarditis was the greatest offender, followed by meningitis, septicemia and pneumonia. The toxins of nephritic origin produced capillary damage and abnormal bleeding in 16 per cent of all cases, an incidence almost equal in importance to that of primary blood dyscrasias.

Kracke,[357] Witts [358] and Moloney [359] emphasize the importance of diagnostic laboratory procedures in the study of hemorrhagic disorders. Haden and Schneider [355] point out that three organs or tissues must be carefully evaluated in every clinical coagulation problem: the liver, which supplies prothrombin, fibrinogen and heparin; the bone marrow, which forms platelets to furnish thromboplastin, and the blood vessels, which may vary in permeability.

The ability of cutaneous capillaries to withstand rupture can be measured by the application of negative pressure to a localized cutaneous area. Using the suction cup method, Franke [360] obtained abnormally low resistance values in patients with obstructive jaundice. A return to normal occurred after treatment with vitamin K. A modification of the suction cup method has been devised by Reid [361] which allows the study of individual capillary loops under direct microscopic vision. Vacek [362] believes that the administration of vitamin P increases capillary resistance if low initial values exist. Vitamin P has been successfully employed by Rapaport [363] to correct abnormally low capillary fragility in allergic children. This vitamin has also been employed with apparent success by Goldfarb [364] in the treatment of psoriasis. No effect

357. Kracke, R. R.: Diagnosis and Treatment of Purpuric Diseases, South. M. J. **34**:56, 1941.

358. Witts, L. J.: The Bleeder and the Laboratory, Lancet **1**:642, 1941.

359. Moloney, W. C.: Clinical Classification and Diagnosis of Hemorrhagic Diatheses, New England J. Med. **225**:933, 1941.

360. Franke, H.: Die Wirkung des Vitamin K auf die Capillarresistenz beim Okklusionsikterus, Klin. Wchnschr. **20**:212, 1941.

361. Reid, J.: Capillary Resistance Test, Glasgow M. J. (supp.) **136**:49, 1941.

362. Vacek, V.: Neuere Erkenntnisse über Vitamin P, Schweiz. med. Wchnschr. **71**:155, 1941.

363. Rapaport, H. G.: Vitamin P and Capillary Fragility, J. Pediat. **18**:321, 1941.

364. Goldfarb, A. E.: Treatment of Psoriasis with Lemon Citrin (Vitamin P), Citrin Lemonade and Ascorbic Acid, Arch. Dermat. & Syph. **43**:536 (March) 1941.

of vitamin P on edema associated with pregnancy was observed by Shute.[365] The oral administration of vitamin P was followed by cessation of bleeding and marked increase in capillary resistance in a case of severe purpura associated with measles which was encountered by Miller.[366]

Rocha e Silva and Dragstedt [367] found that capillary permeability was increased by the injection of tissue extracts. The amount of increase bore a direct relation to the amount of histamine contained in such extracts. Engel [368] noted decreased capillary permeability in dogs, cats and rabbits after severance of sympathetic nerves, despite postoperative vasodilatation.

Glanzmann and collaborators [369] report a case of congenital lack of fibrinogen in a 3 year old boy. There was a tendency to bleed, with giant hematoma characterized by fluid contents. The bleeding and coagulation time of the blood was prolonged. In contrast, in acquired fibrinopenia of childhood there occur jaundice, hepatomegaly, splenomegaly, "streak-like" cutaneous hemorrhages and altered hepatic function. Three patients with a chronic hemorrhagic diathesis characterized by a prolonged bleeding time were studied by Carpenter and Allen.[370] The authors demonstrated differences in the nature of the clots produced in vitro when recalcified plasma from the patients and from control subjects was allowed to coagulate in the presence of a dilute thromboplastin solution. In the pathologic plasma the clot was small and consisted of tenuous threads which rapidly contracted into a firm mass of fibrin. Control plasma from normal persons yielded large clots which underwent only moderate contraction. The authors attribute these differences to deficiency in the "natural thromboplastin" content in the plasma and believe they contribute to the observed bleeding tendency.

Essential Thrombopenic Purpura.—Haden and Schneider [355] report 18 cases of the idiopathic form with platelet counts below 120,000 per

365. Shute, E.: Use of Vitamin P in Oedema of Pregnancy Toxaemia, Canad. M. A. J. **45**:542, 1941.

366. Miller, A. A.: Purpura in Course of Measles: Case Treated with Vitamin P, Brit. J. Child. Dis. **38**:1, 1941.

367. Rocha e Silva, M., and Dragstedt, C. A.: Nature of the Capillary Permeability Factor Present in Extracts of Normal Tissues, Proc. Soc. Exper. Biol. & Med. **46**:303, 1941.

368. Engel, D.: Influence of Sympathetic Nervous System on Capillary Permeability, J. Physiol. **99**:161, 1941.

369. Glanzmann, E.; Steiner, H., and Keller, H.: Konstitutionelle angeborene Afibrinogenämie und Fibrinopenia im Kindesalter, Schweiz. med. Wchnschr. **70**: 1243 and 1261, 1940.

370. Carpenter, G., and Allen, J. G.: Defect in Clot Formation Observed in Three Cases of Chronic Agnogenic Hemorrhagic Disease, Am. J. M. Sc. **202**:655, 1941.

cubic millimeter. Clot retraction was absent and bleeding time was prolonged in each instance. The coagulation time was prolonged in 7 cases. The authors state in interpreting their data:

> It is evident from these figures that the vascular permeability component of the platelets was lacking in all while the thromboplastin factor was lacking in a much smaller number.

Kelly [371] observed a 12 year old girl with purpura, menorrhagia and a platelet count below 10,000 per cubic millimeter for a period of fourteen months without noting any significant change despite roentgen ray therapy over the spleen. Splenectomy was followed by thrombocytosis (over 1,500,000 cells per cubic millimeter). The platelets fell subsequently to a level of 55,000 per cubic millimeter and remained at this level. Despite the low platelet count the menses remained normal. Napier and Das Gupta [372] failed to observe any significant change in the platelet count or the hemorrhagic tendency of a patient with essential thrombopenia after roentgen ray therapy over the spleen, injection of snake venom and oral administration of vitamins K, C and P. Dressler [373] gave vitamin K intravenously to 2 patients with primary thrombopenia and normal prothrombin time and observed a significant but temporary shortening of the bleeding time.

Haden [355] discusses the selection of patients with essential thrombopenic purpura for splenectomy. If the disorder is chronic and there are significant hemorrhagic manifestations, the operation is indicated. In certain cases of the acute form of the disease splenectomy should also be performed. The author reports good results after removal of the spleen in 7 patients with thrombopenic purpura. Wilensky [374] is in general agreement with Haden's views. Reis [375] observed a patient for six years after splenectomy and did not note any recurrence of abnormal bleeding.

After the original report of Troland and Lee that lowering of the platelet counts followed injection into animals of extracts prepared from the spleens of patients with thrombopenic purpura, evidence both in substantiation and in refutation of their conclusions has been offered

371. Kelly, T. C.: Thrombocytopenic Purpura, Pennsylvania M. J. **44**:1442, 1941.

372. Napier, L. E., and Das Gupta, C. R.: A Case of Acute Thrombocytopenic Purpura, Indian M. Gaz. **76**:282, 1941.

373. Dressler, M.: Ueber die Wirkung des Vitamins K (Synkavit) auf die Blutungszeit bei Thrombozytopenien, Schweiz. med. Wchnschr. **71**:483, 1941.

374. Wilensky, A. O.: Indications for Splenectomy in Association with Anemia and Splenomegaly, Surgery **9**:99, 1941.

375. Reis, E.: Beitrag zur Splenektomie bei Purpura haemorrhagica, Zentralbl. f. Chir. **68**:1043, 1941.

by others. Otenasek and Lee [376] support the original work by the report of a significant fall in the platelet counts of rabbits following the intravenous injection of splenic extracts, although in some instances thrombocytosis followed the initial thrombopenia. Confirmatory reports are presented by Rose and Boyer,[377] who gave splenic extracts from 2 patients with purpura intravenously to rabbits, and also by Watson,[378] who observed similar results with three splenic extracts. This author did not observe any consistent alteration in the platelet counts when the extracts were given intraperitoneally to rats. Colmer and Mersheimer,[379] employing two splenic extracts administered according to the method of Troland and Lee, were unable to observe a consistent decrease of the platelet counts in rabbits.

Leonard and Falconer [380] report that purpuric manifestations are not consistently produced in guinea pigs in spite of severe reduction of platelet counts. The thrombopenia was produced by the administration of antiplatelet serum. Guinea pigs on vitamin C–deficient diets treated similarly did not differ from normal animals in the manifestation of purpura. The authors concluded that a deficiency of vitamin C did not contribute to increased capillary permeability in thrombopenic animals. They suggest that a functional rather than an anatomic abnormality of the endothelium might be the major factor in the causation of thrombopenic purpura. Kopeloff and Kopeloff [381] studied the blood platelet levels of animals during anaphylactic shock. A significant lowering of platelet counts occurred in monkeys and other animals after the injection of various antigens. After desensitization of the same animals to the original antigens, a similar degree of thrombopenia developed despite the absence of any anaphylactoid reaction. The authors concluded that the depression of the platelet count is a specific reaction to an antigen not altogether associated with anaphylaxis.

Uihlein and Kendrick [382] noted a progressive fall in the number of circulating platelets in dogs during the course of development of surgical

376. Otenasek, F., and Lee, F. C.: Further Observation on Thrombocytopen, J. Lab. & Clin. Med. **26**:1266, 1941.

377. Rose, H., Jr., and Boyer, L. B.: Thrombocytopen: Confirmatory Report, J. Clin. Investigation **20**:81, 1941.

378. Watson, G. M.: Blood Platelets and Splenic Extracts, Brit. M. J. **1**:704, 1941.

379. Colmer, M. L., and Mersheimer, W. L.: Relation of Splenic Extracts to Etiology of Essential Thrombopenia, Arch. Surg. **43**:422 (Sept.) 1941.

380. Leonard, M. E., and Falconer, E. H.: Experimental Thrombocytopenia Purpura in Guinea Pig, J. Lab. & Clin. Med. **26**:648, 1941.

381. Kopeloff, N., and Kopeloff, L. M.: Blood Platelets in Anaphylaxis, J. Immunol. **40**:471, 1941.

382. Uihlein, A., and Kendrick, D. B., Jr.: Determinations of Blood Platelets During Traumatic Shock: Experimental Study, Proc. Staff Meet., Mayo Clin. **16**:161, 1941.

shock. Splenectomy did not alter the results. Castrodale and collaborators [343] found that in dogs massive doses of estradiol and diethylstilbestrol led to bleeding and thrombopenia. The latter agent was less effective, and the dose required to produce purpura was one hundred times the maximum therapeutic dose for human beings.

From experimental studies Wright [383] concluded that the decrease of blood platelets observed in vitro was due to adhesion of the thrombocytes to the walls of the container. A section of the glass wall of the container was removed and stained and a platelet count was made. A direct relation was observed between the number of platelets on the glass wall and their disappearance from the blood.

Secondary Thrombopenic Purpura.—In the series of cases reported by Perlman and Fox [356] leukemia, aplastic anemia and multiple metastases to the bone marrow were the most frequent causes of secondary thrombopenia encountered at necropsy. Haden and Schneider [355] found the bleeding time prolonged in all but 2 of 26 cases and the coagulation time prolonged in over one half of the cases. Two cases of thrombopenic purpura occurring after the ingestion of acetylisopropylacetylcarbamide (sedormid) are reported by Schäfer,[384] and a case occurring after the ingestion of quinine is recorded by Bais.[385] Burke [386] reports 10 instances of thrombopenia occurring in a series of 3,250 patients during treatment with sulfarsphenamine for venereal diseases. Stephenson, Chambers and Anderson [387] noted 2 deaths in one year in the United States Navy due to blood dyscrasias resulting from the use of arsenical compounds in the treatment of venereal infection. In 1 fatal case agranulocytosis developed after the administration of neoarsphenamine and bismuth subsalycilate; in the other malignant granulocytopenia and thrombopenia with hemorrhage from the nasal membrane occurred after administration of neoarsphenamine and mercury inunctions. A total of 129,295 injections of arsenical compounds were administered during the year. Kirkham and Perlmutter [388] report 1 fatal case of

383. Wright, H. P.: Adhesiveness of Blood Platelets in Normal Subjects with Varying Concentrations of Anticoagulants, J. Path. & Bact. **53**:255, 1941.

384. Schäfer, H.: Thrombopenische Blutungen nach wiederholten Sedormid-Gaben, Med. Klin. **36**:1133, 1940.

385. Bais, W. J.: Another Case of Thrombopenic Purpura Caused by Quinine, Geneesk. tijdschr. v. Nederl.-Indië **81**:2177, 1941.

386. Burke, E. T.: Blood Dyscrasia in the Treatment of Venereal Diseases, Brit. J. Ven. Dis. **17**:125, 1941.

387. Stephenson, C. S.; Chambers, W. M., and Anderson, L. T.: Toxic Effects of Arsenical Compounds as Employed in Treatment of Diseases in the United States Navy, 1939, U. S. Nav. M. Bull. **39**:139, 1941.

388. Kirkham, D., and Perlmutter, M.: Fatal Aplastic Anemia Following Use of Mapharsen: Case Report, Arch. Dermat. & Syph. **43**:111 (Jan.) 1941.

granulocytopenia together with absence of platelets after mapharsen therapy. Weiner and Carter [389] report an instance of thrombopenic purpura associated with miliary tuberculosis of the spleen. Splenectomy was followed by a rise in the platelet count to 500,000 per cubic millimeter and complete recovery of the patient. Thrombopenia associated with discoid lupus erythematosus is reported by Edelman.[390]

Nonthrombopenic Purpura.—Henoch's purpura is discussed by Hampton,[391] who observed in 2 patients exacerbations of the syndrome after the ingestion of specific foods and regressions when these foods were eliminated from the diet. Gastrointestinal roentgenograms revealed changes in the functional activity of the bowel which paralleled the clinical course of the illness. One of the 2 patients studied obtained relief from the syndrome after administration of a 1:1,000 solution of epinephrine hydrochloride. Gonzàlez Batlle [392] reports 2 instances of generalized purpura, hematuria and gastrointestinal bleeding following Mantoux tests on a series of 3,000 children. He chose to classify them as instances of allergic purpura due to sensitivity to tuberculin. A case of the Schönlein-Henoch type of purpura subsequent to smallpox vaccination was encountered by Weingärtner.[393] Spontaneous recovery occurred. The Waterhouse-Friderichsen syndrome is reviewed by Lindsay and his collaborators,[394] Drummond and Tooke [395] and Monfort and Mehrling.[396] Purpura was a feature in each of the 9 new cases reported in these articles. The sudden onset of fulminating toxemia, rapidly developing and extensive purpura, alternating cyanosis and

389. Weiner, J. J., and Carter, R. F.: Acute Thrombocytopenic Purpura Hemorrhagica Associated with Tuberculosis (Miliary) of Spleen: Splenectomy—Recovery, Ann. Surg. **113**:57, 1941.

390. Edelman, M. H.: Thrombocytopenic Purpura Associated with Discoid Lupus Erythematosus and Renal Glomerular Changes, Ann. Int. Med. **15**:116, 1941.

391. Hampton, S. F.: Henoch's Purpura Based on Food Allergy, J. Allergy **12**:579, 1941.

392. Gonzàlez Batlle, P.: Púrpura hemorrágica e intradermoreacción tuberculínica, Bol. Soc. cubana de pediat. **13**:66, 1941.

393. Weingärtner, L.: Purpura Schönlein-Henoch als Folgeerscheinung einer Erstvakzination, Kinderärztl. Praxis **12**:39, 1941.

394. Lindsay, J. W.; Rice, E. C.; Selinger, M. A., and Robins, L.: Waterhouse-Friderichsen Syndrome, Am. J. M. Sc. **201**:263, 1941.

395. Drummond, W. F., and Tooke, T. B., Jr.: Waterhouse-Friderichsen Syndrome: Review of Literature and Report of Two Cases, New Orleans M. & S. J. **94**:11, 1941.

396. Monfort, J. A., and Mehrling, J. H.: Waterhouse-Friderichsen Syndrome: Review of Literature and Report of Case with Autopsy, Am. J. Dis. Child. **62**:144 (July) 1941.

pallor, coma and circulatory collapse with rapidly fatal outcome are emphasized. At necropsy a massive medullary hemorrhage of the adrenal, generally bilateral, is encountered. Meningococci are recovered from the blood stream in a majority of the cases. The therapeutic suggestions of these authors include chemotherapy combined with the use of antimeningococcus serum, administration of epinephrine or of adrenal cortex extract and infusions of physiologic solution of sodium chloride, together with supportive measures. Prompt recognition of this striking syndrome with institution of specific therapy may, it is thought, alter its invariably fatal termination.

Aggeler, Lucia and Thompson [397] discuss primary thrombocytosis and present a syndrome due to occlusion of all arteries arising from the aortic arch which is characterized by thrombocytosis and autohemagglutination. The number of circulating platelets varied between 1,200,000 and 1,500,000 per cubic millimeter. Autoagglutination of red cells was observed at body, room and ice box temperatures.

Hemophilia.—The blood findings in this disease are discussed by Quick [398] with particular emphasis on the methods of diagnosis. As a simple diagnostic test he advocates the determination of the clotting time of oxalated plasma. The plasma is centrifuged, and the clotting time of the supernatant fluid is determined after recalcification. For normal plasma the clotting time by this procedure is approximately two minutes, and for normal whole blood the range is between five and eight minutes. By contrast, hemophilic plasma exhibits a prolonged clotting time of three to five minutes or longer, depending in part on the speed of centrifugation. The observed difference in clotting time of the "platelet-free" plasma is attributed to stability of the platelets, which are slow to disintegrate in hemophilic blood. Efforts to control hemorrhage in hemophilic persons after dental extraction are reported. Van Creveld and Hamer [399] applied a coagulation-promoting globulin obtained from cow's plasma to the tooth socket and obtained favorable results. Heskin [400] notes the reports of other observers that a rubber band placed around a tooth will gradually cut through its attachments. Twenty-six teeth were extracted in this manner with little pain and no hemorrhage in patients with hemophilia.

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397. Aggeler, P. M.; Lucia, S. P., and Thompson, S. H.: Syndrome Due to Occlusion of All Arteries Arising from the Aortic Arch: Report of Case Featured by Thrombocytosis and Autohemoagglutination, Am. Heart J. **22**:825, 1941.

398. Quick, A. J.: Diagnosis of Hemophilia, Am. J. M. Sc. **202**:469, 1941.

399. van Creveld, S., and Hamer, R.: Coagulation-Globulin in Hemorrhages After Extraction of Teeth, Especially in Hemophilic Patients, Am. J. Orthodontics **27**:628, 1941.

400. Heskin, N.: Extraction in Hemophilia, Contact Point **18**:168, 1941.

Oxalic acid given intravenously to 5 hemophilic patients failed to alter the coagulation time, according to Johnson,[401] in contradistinction to the earlier reports of Page, Russell and Rosenthal. Johnson used infusions of "lyophilized" plasma, and de la Maza [402] gave daily small transfusions of whole blood or citrated plasma and observed a shortening of the coagulation time.

Hereditary Hemorrhagic Telangiectasia.—Hereditary hemorrhagic telangiectasia was observed by Alban [403] in members of six generations of one family. Of the 19 affected persons, the majority were women. Griggs and Baker [404] noted severe reactions after transfusion in 1 patient in whom the disease was associated with splenomegaly. Gastroscopic and sigmoidoscopic examinations are reported as "negative" despite gastrointestinal bleeding in another patient examined by these authors. Other instances of this disease are reported by several authors.[405]

Hemostasis and Coagulants.—The important role of the capillaries in the phenomena of hemostasis is considered by Macfarlane.[406] Experimental evidence indicates that in normal subjects the reaction of the capillaries to damage is immediate dilation, then contraction, followed after a variable interval by secondary dilation. In patients with hemorrhagic states, such as thrombopenia purpura, associated with prolonged bleeding times, an abnormal capillary response was observed in that the capillaries failed to contract after damage. After injury the liberation of "histamine-like" substances accounts for the immediate capillary dilation. The flow of blood effects rapid removal of these substances, and the contraction phase then occurs. This enables coagulation of the escaped blood and secure attachment of the clot to the surrounding tissue. With subsequent dilation of the capillaries, the formed clot in large open wounds or the tissue exudate in small wounds prevents any further bleeding. Hemostasis is therefore initiated by capillary con-

401. Johnson, J. B.: Effect of Oxalic Acid Given Intravenously on Coagulation Time in Hemophilia, Proc. Soc. Exper. Biol. & Med. **46**:496, 1941.

402. de la Maza, V.: Hemofilia, Rev. chilena de pediat. **12**:564, 1941.

403. Alban, H.: Hereditary Hemorrhagic Telangiectasia, Northwest Med. **40**:86, 1941.

404. Griggs, D. E., and Baker, M. Q.: Hereditary Hemorrhagic Telangiectasia with Gastro-Intestinal Bleeding, Am. J. Digest. Dis. **8**:344, 1941.

405. Becker, S. W., and Obermayer, M. E.: Telangiectasia Hemorrhagica Hereditaria (Osler's Disease) and Vitiligo, Arch. Dermat. & Syph. **44**:303 (Aug.) 1941. Madden, J. F.: Hereditary Hemorrhagic Telangiectasia, ibid. **44**:540 (Sept.) 1941. Dickman, M.: Hereditary Hemorrhagic Telangiectasia, ibid. **44**: 523 (Sept.) 1941. Blackwood, W.: Two Cases of Benign Cerebral Telangiectasis, J. Path. & Bact. **52**:209, 1941.

406. Macfarlane, R. G.: Critical Review: Mechanism of Hemostasis, Quart. J. Med. **10**:1, 1941.

traction and then maintained by coagulation. Coagulation alone is incapable of arresting bleeding, and platelets function only after hemostasis has taken place. They accelerate clot formation and promote firm retraction of the coagulum.

In hemophilia and some other conditions, such as fibrinopenia, in which coagulation does not occur or a faulty clot is formed during the period of capillary contraction, bleeding recommences on subsequent capillary dilation. In prothrombin deficiency states, faulty clot formation may be associated with a physiologic defect of the capillaries.

Viper venom was efficacious as a control of recurrent hemorrhage of the vitreous (Pradhan and Patwardhan [407]). Edsall [408] concludes that the effectiveness of venom from Russell's viper is due to its synergistic action with cephalin and tissue extracts. In vitro studies demonstrated an action of the venom independent of that of thrombin, prothrombin and platelet material. Rosenfeld and Rubinstein [409] studied the coagulant action of venom from the Australian tiger snake. The material appeared to convert prothrombin to thrombin, behaving like thromboplastin plus calcium, as it promptly clotted citrated plasma. Clots formed in vitro were firmer and withstood lysis thirty-six hours longer than those obtained with venom from the fer-de-lance and from Bothrops jararaca. Venom from Bothrops jararaca has been purified by investigators at the Butantan Institute, São Paulo, Brazil, and can be given intravenously.[410]

An active coagulant has been prepared from rabbit plasma by Parfentjev [411] and its potency confirmed by Taylor, Lozner and Adams.[412] This material appears to act directly on fibrinogen to form thrombin independently of calcium or prothrombin. The effects of the globulin fraction employed were studied in animals by Parfentjev and by Bird,

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407. Pradhan, K. N., and Patwardhan, N. G.: Viper Venom in a Case of Recurrent Hemorrhage in the Vitreous, Indian M. Gaz. **76**:221, 1941.

408. Edsall, G.: Mechanism of the Coagulant Action of Daboia Venom, Am. J. Physiol. **134**:609, 1941.

409. Rosenfeld, S., and Rubinstein, J.: Separation of Coagulant from Toxic Principles of Venom of Australian Tiger Snake: Remarks on Mode of Action of Coagulant, J. Lab. & Clin. Med. **27**:45, 1941.

410. New Antihemorrhagic Agent, Foreign Letters (Brazil), J. A. M. A. **116**:2521 (May 31) 1941.

411. Parfentjev, I. A.: A Globulin-Fraction in Rabbit's Plasma Possessing a Strong Clotting Property, Am. J. M. Sc. **202**:578, 1941.

412. Taylor, F. H. L.; Lozner, E. L.; and Adams, M. A.: The Thrombic Activity of a Globulin Fraction Derived from Rabbit Plasma, Am. J. M. Sc. **202**:582, 1941.

McSwain, Kauer and Glenn.[413] Intravenous administration to animals was accompanied by toxic reactions and in some cases by intravascular clotting. When given orally the substance was nontoxic and effected reduction of the clotting time. Clinically, its oral use proved effective either in reducing the coagulation time or in stopping hemorrhage in gastrointestinal bleeding and in hemophilia, according to Bird and collaborators. Local use of the globulin fraction by Lozner, McDonald, Finland and Taylor [414] stopped bleeding from tooth sockets in patients with hemophilia and other hemorrhagic diatheses. The application of the material in the form of a stable dry powder controlled bleeding from small cutaneous wounds.

The arrest of hemorrhages from the nasal passage by the local use of salt pork has been reported by Cone.[415] Its advantages include availability and low cost. Its effectiveness is attributed to the thromboplastic content and the ease of introduction and efficiency as a nasal pack. The salt probably plays no part in its hemostatic action. A preliminary report by Quastel and Racker [416] deals with the increased thromboplastic activity of muscle extracts obtained from anoxemic areas and from tissue incubated in an oxygen-free atmosphere.

Rabinowitz [417] found that certain amino acids added to the blood of patients with thrombopenic purpura caused normal retraction in vitro. Cystine and methionine were the most effective. The oral administration of cystine failed to produce any significant change in the bleeding tendencies of 2 patients with Werlhof's type of purpura. However, more favorable effects were noted after the use of methionine. Participation of a fat-soluble substance in the normal coagulation of blood is suggested by Macfarlane and his associates.[418]

The mechanism of the fluidity of the menstrual flow was studied by Glueck and Mirsky,[419] who were unable to detect the presence of fibrin-

413. Bird, R. M.; McSwain, B.; Kauer, G. L., Jr., and Glenn, F.: The Clotting Action of Rabbit-Clotting Globulin, Proc. Soc. Exper. Biol. & Med. **48**:730, 1941.

414. Lozner, E. L.; McDonald, H.; Finland, M., and Taylor, F. H. L.: The Use of Rabbit Thrombin as a Local Hemostatic, Am. J. M. Sc. **204**:593, 1941.

415. Cone, A. J.: The Use of Salt Pork in Cases of Hemorrhage, Arch. Otolaryng. **32**:941 (Nov.) 1940.

416. Quastel, J. H., and Racker, E.: Tissue Anoxia and Blood Coagulation, Brit. J. Exper. Path. **22**:15, 1941.

417. Rabinowitz, H. M.: Role of Amino Acids in Clot Retraction; Effect of Methionine in Restoring Normal Clot Retraction and Control of Bleeding in Essential Thrombocytopenia, Am. J. Surg. **51**:366, 1941.

418. Macfarlane, R. G.; Trevan, J. W., and Attwood, A. M. P.: J. Physiol. **99**:7P, 1941.

419. Glueck, H. I., and Mirsky, I. A.: The Clotting Mechanism of Menstrual Fluid, Am. J. Obst. & Gynec. **42**:267, 1941.

ogen, prothrombin, thrombin or any specific anticoagulant in the fluid. Fibrin clots incubated with menstrual blood underwent lysis. The authors suggest that a lytic action takes place on the intrauterine clots, thus accounting for the findings reported. When bleeding from the uterus is excessive, the rate of intrauterine lysis cannot keep up with the hemorrhage and undigested clots are expelled.

Patients with coronary thrombosis were found by Ewing, Cullimore and Blatherwick [420] to have normal plasma clotting times. The only difference observed between the persons with coronary thrombosis and a control group was a longer interval between the appearance of fibrin and the formation of a firm clot. Such observations suggest that patients with such disease may exhibit delayed coagulation rather than a tendency to increased intravascular clot formation.

Extract of adrenal cortex administered to patients before operation and to normal subjects led to a shortening of the coagulation time, averaging 29 and 38 per cent, respectively, according to Reed.[421] The maximum effect occurred in the two hours after administration of the extract, and some measurable changes were still present after twenty-four hours.

Heparin.—Heparin is finding an ever increasing field of clinical usefulness, particularly in the prevention of postoperative thrombosis and embolism and in vascular surgery. In two reviews submitting data on over 1,000 cases Murray [422] and Crafoord and Jorpes [423] conclude that the favorable results outweigh the dangers and disadvantages of its use. Other favorable clinical reports are given by Lam,[424] Bauer [425] and Ravdin.[426]

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420. Ewing, M. E.; Cullimore, O. S., and Blatherwick, N. R.: The Plasma Clotting Time and Serum Calcium of Patients Recovering from Attacks of Coronary Thrombosis, Proc. Soc. Exper. Biol. & Med. **47**:23, 1941.

421. Reed, F. A.: Natural Adrenal Cortex Extract and the Coagulation of Blood, Am. J. Surg. **51**:330, 1941.

422. Murray, G.: Heparin in Thrombosis and Blood Vessel Surgery, Surg., Gynec. & Obst. **72**:340, 1941.

423. Crafoord, C., and Jorpes, E.: Heparin as a Prophylactic Against Thrombosis, J. A. M. A. **116**:2831 (June 28) 1941.

424. Lam, C. R.: Heparin Administration: Methods and Results in Thirty Cases, Ann. Surg. **114**:205, 1941.

425. Bauer, G.: Early Diagnosis of Venous Thrombosis by Means of Venography and Abortive Treatment with Heparin, Acta med. Scandinav. **107**:136, 1941; Venous Thrombosis: Early Diagnosis with the Aid of Phlebography and Abortive Treatment with Heparin, Arch. Surg. **43**:462 (Sept.) 1941.

426. Ravdin, I. S.: Heparin, Am. J. M. Sc. **201**:299, 1941.

The mode of action of heparin has been investigated by Ferguson and Glazko,[427] who express the view that heparin inhibits thromboplastic enzyme activity, resulting in retardation of prothrombin conversion. It is suggested by Chargaff and his associates,[428] on the basis of electrophoretic studies, that heparin reacts with plasma globulins. It is believed that the natural inhibitor in normal blood which prevents clot formation may be a complex formed of heparin and the plasma proteins. Howell [429] restates his suggestion that a heparin-albumin compound is responsible for the normal fluid state of the blood. The presence of this compound is assured by the constant release of heparin into the blood stream.

In summarizing the effects of heparin on blood values other than coagulation, Rigdon and Wilson [430] list increased resistance of red cells to hypotonic solution of sodium chloride, altered sedimentation rate, inhibition of glycolysis and interference with reactions involving complement. They observed that heparin did not affect capillary permeability or interfere with chemotactic or phagocytic activity of the leukocytes of rabbits. The platelet counts in dogs and mice after injection of heparin were studied by Copley and Robb,[431] who observed a reduction in almost every instance. Heparin appeared to have a destructive action on platelets in vitro proportional to its concentration.

Dicoumarin.—The hemorrhagic agent present in spoiled sweet clover has been isolated, identified and synthesized. This work, begun in 1934 by Link and his associates, was completed and reported in a series of papers.[432] Animal experimentation and clinical trial with the new synthetic material were instituted almost immediately. The formula assigned

427. Ferguson, J. H., and Glazko, H. L.: Heparin, Univ. Hosp. Bull., Ann Arbor **7**:27, 1941; Heparin, J. Lab. & Clin. Med. **26**:1559, 1941.

428. Chargaff, E.; Ziff, M., and Moore, D. H.: Studies on the Chemistry of Blood Coagulation, J. Biol. Chem. **139**:383, 1941.

429. Howell, W. H.: Recent Advances in Problem of Blood Coagulation Applicable to Medicine, J. A. M. A. **117**:1059 (Sept. 27) 1941.

430. Rigdon, R. H., and Wilson, H.: Capillary Permeability and Inflammation in Rabbits Given Heparin, Arch. Surg. **43**:64 (July) 1941.

431. Copley, A. L., and Robb, T. P.: Effect of Heparin on Platelet Count in Dogs and Mice, Am. J. Physiol. **133**:248, 1941.

432. Campbell, H. A.; Roberts, W. L.; Smith, W. K., and Link, K. P.: Studies on Hemorrhagic Sweet Clover Disease: Preparation of Hemorrhagic Concentrates, J. Biol. Chem. **136**:47, 1940. Campbell, H. A.; Smith, W. K.; Roberts, W. L., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: Bioassay of Hemorrhagic Concentrates by Following Prothrombin Level in Plasma of Rabbit Blood, ibid. **138**:1, 1941. Campbell, H. A., and Link, K. P.: Studies on Hemorrhagic Sweet Clover Disease: Isolation and Crystallization of Hemorrhagic Agent, ibid. **138**:21, 1941. Stahmann, M. A.; Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: Identification and Synthesis of the Hemorrhagic Agent, ibid. **138**:513, 1941.

to this hemorrhagic agent is, 3, 3′-methylenebis-(4-hydroxycoumarin), and the simpler term suggested for it is dicoumarin.

Studies on dogs and subsequent investigations on human subjects carried out by Bingham, Meyer and Pohle [433] and Butt and his collaborators [434] have demonstrated that the administration of dicoumarin prolongs the coagulation time of the blood. They found, in confirmation of the earlier work of others, that dicoumarin acts by prolonging the blood prothrombin time. No harmful effects were noted after administration of the material in doses which increased the coagulation time to as much as twenty-three minutes and the prothrombin time from twelve to eighteen seconds. Laboratory procedures failed to indicate disturbances of hepatic or renal function or changes in the corpuscular elements of the blood following the ingestion of effective doses of dicoumarin. Unlike the effects of heparin, those of dicoumarin are not manifest until about twenty-four hours after administration. If repeated doses are given, the prothrombin content of the blood becomes progressively diminished. The effect on the prothrombin resulting from a single dose administered to dogs gradually disappears in five to seven days. Large doses cause a greater delay in the return of the prothrombin to normal, but the initial latent period is unaffected by the size of the dose. Transfusion of blood temporarily restores normal prothrombin and coagulation times, and administration of vitamin K is without effect. When fatal doses were given to dogs, no significant pathologic change was observed in any organ except the frequent occurrence of capillary, arteriolar and venule dilatation.

The possible advantages of dicoumarin as a substitute for heparin will depend on further demonstration of its ability to delay or prevent intravascular clotting. Its merits appear to lie in its prolonged action, its relatively low cost and its effectiveness when administered orally.

Prothrombin and Vitamin K.—Pregnancy and the Neonatal Period: The clinical application of results of recent studies on prothrombin and vitamin K has continued to receive much attention. Over one hundred

433. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on Hemorrhagic Agent 3, 3′-Methylenebis-(4-Hydroxycoumarin): Its Effect on Prothrombin and Coagulation Time of Dogs and Humans, Am. J. M. Sc. **202**:532, 1941. Meyer, O. O.; Bingham, J. B., and Pohle, F. J.: Effects of Synthetic Dicoumarin 3, 3′-Methylenebis-(4-Hydroxycoumarin) upon the Prothrombin Time and Coagulation Time, Proc. Central Soc. Clin. Research **14**:8, 1941.

434. Butt, H. R.; Allen, E. V., and Bollman, J. L.: A Preparation from Spoiled Sweet Clover (3, 3′-Methylenebis-[4-Hydroxycoumarin]) Which Prolongs Coagulation and Prothrombin Time of the Blood: Preliminary Report of Experimental and Clinical Studies, Proc. Staff Meet., Mayo Clin. **16**:388, 1941. Barker, N. W.; Butt, H. R.; Allen, E. V., and Bollman, J. L.: Effect of 3, 3′-Methylenebis- (4-Hydroxycoumarin) on Blood Coagulation Factors: Its Probable Clinical Usefulness, Proc. Central Soc. Clin. Research **14**:9, 1941.

and fifty articles on the subject appeared in the last year. Recent general reviews of the development and clinical use of vitamin K include those of Stewart,[435] Almquist,[436] Toohey [437] and others.[438] A discussion of experimental hypoprothrombinemia is given by Rhoads, Warren and Panzer.[439] Prothrombin deficiency in the newborn infant has received much comment, and the subject is reviewed by Savage,[440] Smith,[441] Grossman,[442] Snedeker [443] and others.[444]

It has been clearly demonstrated that physiologic hypoprothrombinemia develops in the immediate neonatal period. At birth the prothrombin value averages 70 to 75 per cent of that of normal adults.

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435. Stewart, J. D.: Clinical Significance of Prothrombin Deficiency and Its Treatment, Ann. Surg. **114**:907, 1941.

436. Almquist, H. J.: Vitamin K, Physiol. Rev. **21**:194, 1941.

437. Toohey, M.: Prothrombin: Its Estimation, Clinical Significance and the Therapy of Hypoprothrombinaemia, Irish J. M. Sc., 1941, p. 509.

438. Freeman, S., and Grodins, F. S.: Recent Studies of Factors Involved in Coagulation, Including Review of Vitamin K, Surg., Gynec. & Obst. **72**:417, 1941. Kark, R., and Souter, A.: Hypoprothrombinemia and Avitaminosis in Man, Brit. M. J. **2**:190, 1941. Chute, R.: Value of Vitamin K in Treatment of Abnormal Bleeding, New England J. Med. **224**:360, 1941. Quick, A. J.: Contribution of Laboratory to Treatment of Hemorrhage, Illinois M. J. **79**:346, 1941. Acuña, M., and Lobo, A. A.: Determinación de la protrombina sangúinea: su valor clínico, Prensa méd. argent. **28**:1091, 1941.

439. Rhoads, J. E.; Warren, R., and Panzer, L. M.: Experimental Hypoprothrombinemia, Am. J. M. Sc. **202**:847, 1941.

440. Savage, H.: Development of Vitamin K and Its Clinical Use in Neonatal Period, Arch. Dis. Childhood **16**:67, 1941.

441. Smith, C. H.: Recent Advances in Diagnosis and Treatment of Blood Disorders in Infancy and Childhood, M. Clin. North America **25**:659, 1941.

442. Grossman, A. M.: Coagulation Defects in Infancy and Childhood: Frequency of Hypoprothrombinemic States and Their Treatment with Vitamin K, Reclassification of Hemorrhagic Hypoprothrombinemia Neonatorum, J. Pediat. **19**:205, 1941.

443. Snedeker, L.: Hemorrhagic Disease of Newborn: Report of Three Hundred and Fifty-Eight Cases, J. Pediat. **19**:1, 1941.

444. Quick, A. J.: Prevention of Bleeding in Newborn, Wisconsin M. J. **40**:581, 1941. Bustamante, E. W.: Vitamin K y sus aplicaciones en pediatria, Rev. chilena de pediat. **1**:47, 1941. Rouhunkoski, M., and Saksela, N.: Hypoprothrombinemia Neonatorum and Its Relations to Vitamin K, Acta obst. et gynec. Scandinav. **21**:203, 1941. Ortega, A. R.: La vitamina K y su empleo en clínica: Revisión de la literatura, Rev. chilena de pediat. **1**:165, 1941. Norris, R. F., and Bennett, M. C.: Plasma Prothrombin Values of Mothers and Infants at Delivery: Further Studies Including Comparative Values of Umbilical Arteries and Veins, Surg., Gynec. & Obst. **72**:758, 1941. Fanconi, G.: Blutungsübel des Kindesalters, die auf einer Störung des Gerinnungsvorganges beruhen, unter besonderer Berücksichtigung des K-Vitamins, Schweiz. med. Wchnschr. **71**:185, 1941. Fiechter, N.: Hypoprothrombinämie und hämorrhagische Diathese des Neugeborenen und ihre Beziehungen zum Vitamin K, Monatschr. f. Geburtsh. u. Gynäk. **111**:1, 1940.

It falls rapidly, to reach a minimum level between the second and the fifth day of life, and during this period a hemorrhagic disorder may become manifest. Usually a return to the birth level takes place between the fourth and the sixth day, with a subsequent continued rise for about ten to fourteen days. Values equal to those of normal adults may not be reached until one and one half months of age, according to Plum.[445]

A seasonal factor in the incidence of hypoprothrombinemia of newborn infants has been demonstrated by several observers.[446] In general, values tend to be lower during the winter months. Javert and Macri [447] observed an upward trend of the blood prothrombin value throughout pregnancy. Thirty of 200 pregnant women studied by them had prothrombin values which were less than 70 per cent of normal and were regarded by the authors as representing instances of avitaminosis K. Two separate declines of the prothrombin level were observed during pregnancy; the first occurred at about the fourth week, during the period of morning sickness, and was attributed to deficient dietary intake of vitamin K; the second was noted usually during the twenty-eighth week and was presumably explained by the demands of the fetus. The dietary intake of pregnant women was studied by Astrowe and Palmerton [448] in relation to the subsequent prothrombin values of the mothers and their infants. No relation was found between the level of prothrombin of infants and either an adequate or a deficient intake of vitamin K by the mothers.

Vitamin K given to mothers during labor has proved successful in lessening the fall in prothrombin in the neonatal period. The reports of Bohlender and Rosenbaum [449]; Beck, Taylor and Colburn,[450] and others [451]

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445. Plum, P.: K-Vitaminmangel bei Kindern, Deutsche med. Wchnschr. **66**:1389, 1940.

446. (*a*) Salomonsen, L.: Hemorrhagic Disease of Newborn Due to Hypoprothrombinemia, Nord. med. **7**:1309, 1940; (*b*) On the Prevention of Hemorrhagic Disease of Newborn by Administration of Cow's Milk During the First Two Days of Life, Acta pædiat. **28**:1, 1940. (*c*) Huber, C. P., and Shrader, J. C.: Blood Prothrombin Level in Newborn, Am. J. Obst. & Gynec. **41**:566, 1941.

447. Javert, C. T., and Macri, C.: The Prothrombin Concentration in Normal Pregnancy, Am. J. Obst. & Gynec. **42**:415, 1941.

448. Astrowe, P. S., and Palmerton, E. S.: Clinical Studies on Vitamin K in Newborn Infants, J. Pediat. **18**:507, 1941.

449. Bohlender, G. P., and Rosenbaum, W. M.: Antepartum Use of Vitamin K in the Prevention of Prothrombin Deficiency in the Newborn, J. A. M. A. **116**:1763 (April 19) 1941.

450. Beck, A. C.; Taylor, E. S., and Colburn, R. F.: Vitamin K Administered to Mother During Labor as Prophylaxis Against Hemorrhage in Newborn Infant, Am. J. Obst. & Gynec. **41**:765, 1941.

451. Valentine, E.; Reinhold, J., and Schneider, E.: Effectiveness of Prenatal Administration of 2-Methyl-1, 4-Naphthoquinone in Maintaining Normal Pro-

(*Footnote continued on next page*)

are representative. Vitamin K was administered orally at periods ranging from five minutes to forty-eight hours prior to delivery. The prothrombin levels at birth were above 90 per cent of the adult normal value, and there was no subsequent decline. The incidence of hemorrhagic manifestation in the series reported by Beck and co-workers was 0.5 per cent of 1,022 infants whose mothers had been given vitamin K during labor. Thirty-seven infants born prematurely were included in this group, and of these, abnormal bleeding occurred in 5.4 per cent. In a control group of 1,037 infants whose mothers had not received vitamin K the incidence of hemorrhage was 2 per cent. The use of vitamin K is particularly indicated when premature birth of the infant is expected, in cases of prolonged labor or when there is a prospect of any operative type of delivery. In these circumstances intracranial hemorrhage is especially likely to occur, according to Ross and Malloy.[452] It is advised by Lawson, Wyvell and Branning [453] that vitamin K be given orally during the last month of pregnancy, but McCready and his associates [454] report that if treatment has been omitted in the days immediately preceding delivery, there is little effect of previous administration on the prothrombin level of an infant. It is generally recommended that every patient in labor should receive vitamin K, either orally or parenterally and that the dose should be repeated every six to eight hours throughout the duration of labor.

Administration of vitamin K to women during labor reduced the incidence of retinal hemorrhages, according to Maumenee, Hellman and Shettles [455] and Pray, McKeown and Pollard.[456] Javert and Macri [457]

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thrombin Level in Infants, Am. J. M. Sc. **202**:359, 1941. Mull, J. W.; Bill, A. H., and Skowronska, H.: Effect on Newborn of Vitamin K Given to Mothers in Labor, J. Lab. & Clin. Med. **26**:1305, 1941.

452. Ross, S. G., and Malloy, H. T.: Blood Prothrombin in Newborn: Effect of Vitamin K upon Blood Prothrombin and upon Hemorrhagic Disease of Newborn, Canad. M. A. J. **45**:417, 1941.

453. Lawson, R. B.; Wyvell, D. B., and Branning, W. S.: Vitamin K in Prevention and Treatment of Hemorrhagic Disease of Newborn, North Carolina M. J. **2**:234, 1941.

454. McCready, R. L.; Callahan, E. T., and Grandin, D. J.: Parenteral Vitamin K Therapy in Ante-Partum Women and Its Effects on the Infants' Prothrombin Levels: A Preliminary Report, Am. J. Obst. & Gynec. **42**:398, 1941.

455. Maumenee, A. E.; Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in Newborn Infants: Effect of Antenatal Administration of Vitamin K on Incidence of Retinal Hemorrhage, Bull. Johns Hopkins Hosp. **68**:158, 1941.

456. Pray, L. G.; McKeown, H. S., and Pollard, W. E.: Hemorrhagic Diathesis of Newborn: Effects of Vitamin K Prophylaxis and Therapy, Am. J. Obst. & Gynec. **42**:836, 1941.

457. Javert, C. T., and Macri, C.: Prothrombin Concentration and Mineral Oil, Am. J. Obst. & Gynec. **42**:409, 1941.

found that the daily use of liquid petrolatum by pregnant women resulted in a lowering of the prothrombin level.

Hemorrhages of the newborn are classified by Edsall [458] as due either to a low prothrombin level or to causes other than defects in the intrinsic coagulation mechanism, such as transitory bleeding from the intestinal tract or rupture of minor blood vessels during delivery. Vitamin K is of specific value in the treatment of hemorrhages due to hypoprothrombinemia. If the blood prothrombin value is 30 per cent of normal, hemorrhage is common, and if the level falls below 15 per cent, bleeding is apt to be severe.

Vitamin K may be administered effectually by oral, intramuscular or intravenous route and can be absorbed through the skin, according to Russell and Page [459] and deBeer and collaborators [460] when applied in an ointment base. Vitamin K introduced into the blood stream causes a rapid rise of prothrombin. A significant elevation is said to occur after thirty minutes, and in twenty-four hours levels of 70 to 100 per cent of normal may be attained in spite of extremely low initial values. Kove and Siegel [461] found that 1 mg. doses produced a maximal prothrombin response. Once a hemorrhagic tendency has become manifest, the immediate parenteral use of vitamin K is advocated by Willumsen, Stadler and Owen [462] and Leidenheimer and Albritton.[463] The advisability of transfusion as supplementary therapy is advised by Arden,[464] Damm [465] and Kove and Siegel.[466] In the replacement of

458. Edsall, G.: Prothrombin Level in Early Infancy: Its Relation to Hemorrhage and Other Neonatal Disorder, New England J. Med. **224**:762, 1941.

459. Russell, H. K., and Page, R. C.: Effect of Topical Application of 2-Methyl-1, 4-Naphthoquinone on Prothrombin Level of Newborn Infants, Am. J. M. Sc. **202**:355, 1941.

460. deBeer, E. J.; Drektar, L., and Flusser, B.: Routes of Administration of Material Capable of Acting as Vitamin K, Proc. Soc. Exper. Biol. & Med. **46**:535, 1941.

461. Kove, S., and Siegel, H.: Prothrombin in the Newborn Infant: IV. Further Observations on the Prothrombin Response to Intravenous Administration of Water-Soluble Naphthoquinone, J. Pediat. **19**:503, 1941.

462. Willumsen, H. C.; Stadler, H., and Owen, P. A.: Comparative Effects of Vitamin K and Whole Blood on Prothrombin Deficiency of Newborn Infant, Proc. Soc. Exper. Biol. & Med. **47**:116, 1941.

463. Leidenheimer, H., Jr., and Albritton, A. S.: Studies on Bleeding Tendency and Vitamin K Therapy in Newborn Children, New Orleans M. & S. J. **93**:464, 1941.

464. Arden, F.: Hemorrhage, Anemia and Jaundice of Newborn, M. J. Australia **2**:343, 1941.

465. Damm, P. N.: Hemorrhagic Diathesis in Newborn in Regard to Treatment with Transfusion, Ugesk. f. læger **102**:620, 1940.

466. Kove, S., and Siegel, H.: Prothrombin in the Newborn Infant: II. Prothrombin Response to Water-Soluble Naphthoquinone Administered Intravenously; III. On the Nature of Prothrombin in the Newborn Infant, J. Pediat. **18**:764, 1941.

lost blood and the combat of shock, the indications for transfusion are matters for individual decision. That use of transfused blood as a source of prothrombin is not an effective means of elevating the infant's value above the hemorrhagic zone was reported by Lawson [467] and Gellis and Lyon.[468] Plum [445] succeeded in raising the prothrombin level of bleeding infants by only 1 to 20 per cent by means of transfusions of 20 to 40 cc. of blood. The effect lasted twelve to twenty-four hours. Macpherson [469] obtained similar results and noted that after administration of vitamin K alone, the rise in prothrombin in the infant's blood was higher than when the vitamin was used in combination with blood transfusion. Whole blood given intramuscularly or subcutaneously exerted no effect on the prothrombin level according to Willumsen, Stadler and Owen.[462] The intravenous injection of serum was likewise ineffective.

Gellis and Lyon [470] confirmed the observation of Salomonsen [471] that supplementary feeding of cow's milk instituted soon after birth prevents the usual degree of physiologic fall of prothrombin. They found that the earlier evaporated milk was fed, the less was the subsequent decline in prothrombin. These observations are explained by the correspondingly early invasion of the intestinal tract by bacteria which serve as a natural source of vitamin K.

No qualitative differences between the prothrombin of newborn infants and that of adults were detected by Kove and Siegel.[466] By a dilution procedure, identical patterns of lessened activity were obtained both with blood of normal adults and with the blood of infants with hypoprothrombinemia.

No correlation between hypoprothrombinemia and bilirubinemia in the newborn was found by Norris and Bennett.[472]

Most authors in reporting their studies of hypoprothrombinemia of the newborn employ, often with minor modifications, the method of Smith, Quick or Kato for the determination of the prothrombin time.

467. Lawson, R. B.: Treatment of Hypoprothrombinemia (Hemorrhagic Disease) of Newborn Infants, J. Pediat. **18**:224, 1941.

468. Gellis, S. S., and Lyon, R. A.: Effect of Intravenous Injections of Whole Blood on Prothrombin Index of Newborn Infants, Am. J. Obst. & Gynec. **42**:519, 1941.

469. Macpherson, A. I. S.: Treatment of Hemorrhagic Disease of Newborn, Brit. M. J. **2**:433, 1941.

470. Gellis, S. S., and Lyon, R. A.: Influence of Diet of Newborn on Prothrombin Index, J. Pediat. **19**:495, 1941.

471. Salomonsen (footnote 446 *a* and *b*).

472. Norris, R. F., and Bennett, M. C.: Comparison of Prothrombin and Bilirubin Values in Umbilical Artery and Vein at Delivery, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **3**:353, 1941.

Bruchsaler,[473] Huber and Shrader,[474] Lawson,[467] Karabin and Anderson,[475] Russell and Page [459] and Innes and Davidson [476] give details of convenient bedside methods employing whole blood. Lung preparations as a source of thromboplastin are used by Bruchsaler and by Huber and Shrader and venom from Russell's viper by the two last-named pairs of authors.

Obstructive Jaundice and Hepatic Disease: In the management of jaundiced patients and those with biliary fistula the use of vitamin K has earned a permanent place.[477] In the surgical patient with jaundice avitaminosis K is the result not so much of deficiency disease as of faulty absorption. Coller and Farris [478] emphasize that the aspiration of bile by any suction apparatus leads to defective absorption of vitamin K in the same manner as obstruction of the bile ducts. Allen and Livingstone [479] observed that the prothrombin of the blood did not fall after operations elsewhere than on the biliary tract in which a variety of anesthestic agents were employed. In contrast a sharp postoperative decline was observed in patients with obstructive jaundice. The patients receiving the least preoperative treatment with vitamin K showed the earliest fall. Experimental studies on dogs, according to Allen, Kable and Livingstone,[480] likewise failed to demonstrate any prolongation of the prothrombin time following use of a variety of anesthetic agents. They found chloroform to be the exception, with a reduction of prothrombin values to 75 per cent or more in twenty-four hours.

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473. Bruchsaler, F. S.: Vitamin K and Prenatal and Postnatal Prevention of Hemorrhagic Disease in Newborn Infants, J. Pediat. **18**:317, 1941.

474. Huber, C. P., and Shrader, J. C.: Simplified Determination of Blood Prothrombin Levels in Newborn, J. Lab. & Clin. Med. **26**:1379, 1941.

475. Karabin, J. E., and Anderson, E. R.: Simplified Micro Test of Plasma Prothrombin, J. Lab. & Clin. Med. **26**:723, 1941.

476. Innes, J., and Davidson, L. S. P.: Simple Method of Estimating Prothrombin Capillary Blood, Brit. M. J. **1**:621, 1941.

477. Reid, J.: Prothrombin Deficiency in Diseases of Liver and Bile Passages and Its Treatment with Synthetic Vitamin K, Brit. M. J. **1**:579, 1941. Reed, G. S.: The Use of Vitamin K in Obstructive Jaundice, New York State J. Med. **41**:1653, 1941. Dario Quiroz, J.: Nuestros conocimientos actuales sobre la vitamina K, Rev. san mil, Asunción **14**:41, 1940. Tage-Hansen, E.: Aus Forschung und Erfahrung: Ueber K-Avitaminose und ihr Behandlung, Hippokrates **12**:141, 1941. Dam, H.: Vitamin K, Am. J. Pharm. Educ. **5**:273, 1941.

478. Coller, F. A., and Farris, J. M.: The Management of Jaundiced Patients with Special Reference to Vitamin K, Surg., Gynec. & Obst. **73**:21, 1941.

479. Allen, J. G., and Livingstone, H.: Postoperative Hypoprothrombinemia and Anesthesia, Arch. Surg. **42**:522 (March) 1941.

480. Allen, J. G.; Kable, V., and Livingstone, H.: Effects of Anesthetic Agents on Prothrombin Concentrations in Experimental Animals, Anesth. & Analg. **20**:156, 1941.

It has been noted that the response of prothrombin to vitamin K administration in the presence of intrahepatic disease is poor and is reported by Olwin [481] to be in marked contrast to that occurring in the presence of jaundice with extrahepatic obstruction. Such variations in the response of prothrombin to the administration of vitamin K have been used by Lord and Andrus [482] to differentiate jaundice due to stone, tumor or stricture from that associated with diffuse hepatic disease. The method measures the change of the prothrombin value of the blood in a given period after the parenteral administration of 2 mg. of menadione. Failure to obtain a rise of more than 10 per cent in twenty-four hours from the pretreatment prothrombin level or more than 15 per cent in forty-eight to seventy-two hours is believed to signify intrahepatic disease. The response to vitamin K has been used as the basis of a hepatic function test. The test is a measure of the ability of the liver to produce prothrombin. This function apparently does not parallel the capacity to synthesize hippuric acid. Poor agreement between the results of the two tests is reported by Lucia and Aggeler [483] and Kark and co-workers.[484] Rosenberg and Soskin,[485] in a report on the cephalin-cholesterol flocculation test as a measure of hepatic function, state that 37 to 100 patients with hepatic damage had a decreased prothrombin value, whereas the cephalin-cholesterol procedure tested on the same subjects yielded positive results in 98 per cent.

Miscellaneous Disorders: Hypoprothrombinemia is reported by Mazzini and Meyer [486] in 14 cases of gastric ulcer. Improvement in the bleeding tendency resulted after institution of vitamin K therapy. A specimen of liver for biopsy was taken in one third of the cases, and signs of early cirrhosis or cholecystitis were found in all instances.

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481. Olwin, J. H.: The Differentiation of Surgical Jaundice from Severe Damage of the Liver (Subacute Yellow Atrophy) Clinically Simulating It, Arch. Surg. **43**:633 (Oct.) 1941.

482. Lord, J. W., Jr., and Andrus, W. DeW.: Differentiation of Intrahepatic and Extrahepatic Jaundice: Response of the Plasma Prothrombin to Intramuscular Injection of Menadione (2-Methyl-1, 4-Naphthoquinone) as a Diagnostic Aid, Arch. Int. Med. **68**:199 (Aug.) 1941.

483. Lucia, S. P., and Aggeler, P. M.: Influence of Liver Damage on Plasma Prothrombin Concentration and Response to Vitamin K, Am. J. M. Sc. **201**:326, 1941.

484. Kark, R.; White, F. W.; Souter, A. W., and Deutsch, E.: Blood Prothrombin Levels and Hippuric Acid Excretion Liver Function Test in Liver Disease, Proc. Soc. Exper. Biol. & Med. **46**:424, 1941.

485. Rosenberg, D. H., and Soskin, S.: Comparison of Cephalin-Cholesterol Flocculation Test with Various Criteria of Liver Function, with a Note on the Significance of Hyperexcretion of Hippuric Acid, Am. J. Digest. Dis. **8**:421, 1941.

486. Mazzini, O. F., and Meyer, G. R.: Vitamin K y cirugia: Modificaciones de la protrombinemia, Bol. y trab., Acad. argent de cir. **25**:18, 1941.

Hypoprothrombinemia was encountered by Lord and Andrus [487] in a series of 36 patients with toxic goiter in the postoperative period. The values increased spontaneously to normal within one week after operation.

Plasma prothrombin studies were carried out by Tocantins and Hause [488] on 31 patients with pneumonia. In approximately one half of all patients at some time during the disease the values were less than 50 per cent of normal, with a tendency for the lowest level to occur early in the course of the infection. The responses to treatment with vitamin K were not consistent in the patients tested.

Pulmonary tuberculosis was studied from the viewpoint of the prothrombin content of the blood by Savacool,[489] Sheely,[490] Bauer [491] and Kaplan.[492] Savacool and Sheely state that patients with the disease in active form possess significantly low prothrombin values. The level of the prothrombin appears to bear an inverse relation to the status of patients with pulmonary tuberculosis as measured by clinical and roentgenologic criteria and is a more accurate index of the activity of the disease process than is the sedimentation rate. In patients suffering with hemoptysis lowered prothrombin values were frequently, but not consistently, found. Vitamin K therapy may prove of value in the management of some patients with pulmonary hemorrhage. Kaplan [492] found normal prothrombin values in patients with hemoptysis. Bauer [491] did not observe any parallel between severity of tuberculosis and the degree of hypoprothrombinemia.

Evidence of vitamin K deficiency was found in 9 of 30 patients with tropical sprue studied by Diaz y Rivera.[493] Of three preparations exhibiting vitamin K activity, only menadione appeared capable of maintaining normal prothrombin levels in patients with nontropical sprue, according to Allen.[494]

487. Lord, J. W., Jr., and Andrus, W. DeW.: Changes in Liver Associated with Hyperthyroidism with Study of Plasma Prothrombin Level in Immediate Postoperative Period, Arch. Surg. **42**:643 (April) 1941.

488. Tocantins, L. M., and Hause, W. A.: The Behavior of Plasma Prothrombin in Pneumonia, Am. J. Clin. Path. **11**:849, 1941.

489. Savacool, J. W.: Prothrombin Studies in Pulmonary Tuberculosis, Am. J. M. Sc. **201**:830, 1941.

490. Sheely, R. F.: Prothrombin Deficiency in Pulmonary Tuberculosis: Clinical Significance in Hemoptysis, J. A. M. A. **117**:1603 (Nov. 8) 1941.

491. Bauer, G.: Ueber Hypoprothrombinämie, Blutungsbereitschaft und Hämoptöe bei Lungentuberculose und ihre Beeinflussung durch Vitamin K, Deutsche med. Wchnschr. **67**:594, 1941.

492. Kaplan, R. H.: Use of Vitamin K in Hemoptysis in Pulmonary Tuberculosis, M. Bull. Vet. Admin. **18**:48, 1941.

493. Diaz y Rivera, R. S.: Prothrombin Time in Tropical Sprue: Analysis of Thirty Cases, Puerto Rico J. Pub. Health & Trop. Med. **17**:128, 1942.

494. Allen, J. G.: Comparative Prothrombin Responses to Vitamin K and Several of Its Substitutes in a Case of Nontropical Sprue, New England, J. Med. **224**:195, 1941.

Warner, Spies and Owen [495] add supporting evidence to the view that dietary deficiencies of vitamin K severe enough to produce clinical hypoprothrombinemia are rarely encountered. They report that of 48 patients with signs of deficiencies of some part of the vitamin B complex, only 6 possessed prothrombin levels below 80 per cent of normal. In a control group of 37 patients without evidence either of specific vitamin deficiencies or of hepatic disease, 10 had values below 80 per cent of normal.

A case of idiopathic hypoprothrombinemia in a patient first thought to have hemophilia and observed throughout fifteen consecutive hospital admissions is presented by Rhoads and Fitz-Hugh.[496] The marked prolongation of the prothrombin time was not affected by vitamin K administration. In addition, it appeared that a qualitative deficiency of fibrinogen was also present, as evidenced by an unusual resistance to the action of thrombin. There were no evidences of hepatic disease or of excess antithrombin, antiprothrombin or heparin. The authors were unable to identify this condition with any of the known hemorrhagic diatheses.

Abbott and Holden [497] observed hypoprothrombinemia following prolonged vomiting, intestinal intubation and formation of an intestinal fistula. Vitamin K and bile salts proved effective in overcoming the conditioned deficiency. Allen and Vermeulen [498] present evidence of the storage of vitamin K. In a patient with a bile fistula the authors observed a direct relation between the duration of administration of vitamin K and the period that elapsed after withdrawal of the drug before a decline of the prothrombin resulted. Lowering of the prothrombin time may not occur for a month or longer after the institution of a biliary fistula, whereas in cases of obstructive jaundice such a decrease may take place rapidly. These observations are explained, respectively, by storage of vitamin K and by associated hepatic damage.

Pancreatic achylia was produced in cats by Sproul and Sanders,[499] and subsequent lowering of the prothrombin values of the animals was

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495. Warner, E. D.; Spies, T. D., and Owen, C. A.: Hypothrombinemia and Vitamin K in Nutritional Deficient States, South. M. J. **34**:161, 1941.

496. Rhoads, J. E., and Fitz-Hugh, T., Jr.: Idiopathic Hypoprothrombinemia—An Apparently Unrecorded Condition, Am. J. M. Sc. **202**:662, 1941.

497. Abbott, W. E., and Holden, W. D.: Hypoprothrombinemia in Intestinal Disorders, Am. J. Surg. **53**:215, 1941.

498. Allen, J. G., and Vermeulen, C.: Destruction of Prothrombin and Storage of Vitamin K, Arch. Surg. **42**:969 (June) 1941.

499. Sproul, E. E., and Sanders, E. K.: Effect of Pancreatic Achylia on Vitamin K Absorption and Prothrombin Time, Am. J. Physiol. **135**:137, 1941.

noted. The absorption of two vitamin K compounds through the intestinal tract is reported by Morse and Schmidt [500] in rats without the presence of bile, in bile fistula animals. The absorption was sufficient to elevate the prothrombin values.

Substances Possessing Vitamin K Activity: The routes of administration and the effective doses of various vitamin K preparations have been widely studied. To the most active compound, 2-methyl-1,4-naphthoquinone, has been assigned the nonproprietary name menadione.[501] The lethal dose of menadione for rabbits is placed at three to five hundred times the minimum antihemorrhagic dose as determined by chick assay by Fromherz.[502] Oral administration of this substance in patients with hypoprothrombinemia results in a measurable response within one-half to one hour (Anderson, Karabin, Udesky and Seed [503]). Percutaneous administration of a 1 per cent solution of menadione in cod liver oil as used by Fantl and Corkill [504] or in an ointment base as employed by Russell and Page [459] is an effective mode of therapy. The speed of prothrombin response after oral and after parenteral administration has been compared by Tocantins and Jones [505] and Stewart.[506] The adaptation of menadione to intravenous use is discussed by Olwin.[507] He observed no untoward effects after the injection of single doses of 20 mg. or of 2 mg. daily for periods up to three months. A suspension of naturally occurring vitamin K_1 has been prepared in dextrose solution by Seligman, Hurwitz, Frank and Davis.[508] Prolonged therapeutic

500. Morse, L. M., and Schmidt, C. L. A.: Absorption of 2-Methyl-1, 4-Naphthoquinone and Phthiocol by Bile Fistula Rats, Proc. Soc. Exper. Biol. & Med. **46**:415, 1941.

501. Menadione, Noneproprietary Term for the Substance 2-Methyl-1, 4-Naphthoquinone, report of the Council on Pharmacy and Chemistry, J. A. M. A. **116**:1054 (March 15) 1941.

502. Fromherz, K.: Pharmakologische Wirkungen von Vitamin K-Präparaten, Ztschr. f. Vitaminforsch. **11**:65, 1941.

503. Anderson, E. R.; Karabin, J. E.; Udesky, H. L., and Seed, L.: Oral Administration of Synthetic Vitamin K (2-Methyl-1, 4-Naphthoquinone), Surgery **9**:361, 1941.

504. Fantl, P., and Corkill, A. B.: Percutaneous Treatment of Vitamin K Deficiency, M. J. Australia **2**:540, 1941.

505. Tocantins, L. M., and Jones, H. W.: Hypoprothrombinemia: Effect of Peroral and Parenteral Administration of Synthetic Vitamin K Substitute (2-Methyl-1, 4-Naphthoquinone), Ann. Surg. **113**:276, 1941.

506. Stewart, J. D.: Oral and Parenteral Use of Synthetic Vitamin K-Active Substances in Hypoprothrombinemia, Surgery **9**:212, 1941.

507. Olwin, J. H.: Intravenous Use of Vitamin K, J. A. M. A. **117**:432 (Aug. 9) 1941.

508. Seligman, A. M.; Hurwitz, E.; Frank, H. A., and Davis, W. A.: Intravenous Use of Synthetic Vitamin K_1, Surg., Gynec. & Obst. **73**:686, 1941.

effects were observed after its intravenous administration in large doses. Many other compounds with vitamin K activity exert important antihemorrhagic effects.[509]

Substances Possessing Thromboplastic Activity: Thromboplastin preparations made by Quick's method and stored in a refrigerator retained their activity for as long as six months, according to a report by Poncher, Ricewasser and Kato.[510] These authors [511] state that when the material was suspended in physiologic solution of sodium chloride it remained potent for one hundred and twelve days. Thromboplastin prepared from the brains of stillborn infants was found by Sherber [512] to keep without loss of activity for periods up to six months after extraction in physiologic solution of sodium chloride. The stability of such material is not adversely affected by extraction and suspension in a 1:40 molar concentration of calcium chloride in physiologic solution of sodium chloride. Owen and Toohey [513] found thromboplastic activity to be unimpaired when macerated brain was suspended in physiologic solution of sodium chloride for periods over thirty days and stored in air-tight containers at refrigeration temperatures. Moena Gomez [514] obtained the most rapid coagulation time for plasma by using 0.03 to 0.05 cc. of 0.5 per cent calcium chloride solution and 0.1 to 0.5 cc. of thromboplastin in place of the concentrations for the prothrombin time technic given by Quick. The optimal coagulation of plasma occurs at a p_H range of 6 to 8, according to Tanturi and Banfi.[515] They advocate the use of barium sulfate for removing prothrombin from plasma. The resultant prothrombin-free plasma is neutral in reaction and may be

509. Doisy, E. A.: Antihemorrhagic Compounds, Proc. Staff Meet., Mayo Clin. **16**:293, 1941. Sharp, E. A.; Vonder Heide, E. C., and Good, W. H.: Vitamin K Activity of Menadione and 4-Amino-2-Methyl-1-Naphthol in Hypoprothrombinemia, J. Lab. & Clin. Med. **26**:818, 1941. Stewart.[506] Olwin.[507]

510. Poncher, H. G.; Ricewasser, J. C., and Kato, K.: Relative Stability and Potency of Thromboplastins for Prothrombin Tests, J. Lab. & Clin. Med. **27**:385, 1941.

511. Poncher, H. G.; Ricewasser, J. C., and Kato, K.: Stability of Quick's Thromboplastic Solutions for Prothrombin Tests, Am. J. Clin. Path., Tech. Supp. **11**:110, 1941.

512. Sherber, D. A.: A Technique for Determination of Prothrombin Time, J. Lab. & Clin. Med. **26**:1058, 1941.

513. Owen, T. K., and Toohey, M.: Estimation of Prothrombin, Lancet **1**:724, 1941.

514. Moena Gomez, A.: Algunas observaciones a la técnica de Quick de titulación de la protrombina, Rev. méd. de Chile **69**:580, 1941.

515. Tanturi, C. A., and Banfi, R. F.: Determinación de la protrombina en la sangre, Bol. Inst. clin. quir. **17**:119, 1941.

added to pathologic plasma when dilution is desirable. Ferguson and Glazko [516] demonstrate that a natural antithrombin is present in plasma by obtaining increased yields of thrombins with maximal calcium and thromboplastin concentrations if the prothrombin is diluted. Ferguson [517] shows citrated prothrombin to be stable in the presence of thrombin. The two substances can coexist without mutual destruction.

Additional contributions on the thromboplastic activity of venom from Russell's viper have been published by Page and Russell [518] in America and Crosbie and Scarborough [519] and Hobson and Witts [520] in England. Page and Russell emphasize the standardized nature of the material and its relative stability in the dry state. The determination of the clotting time is facilitated by the clear solution provided by venom as a thromboplastic material. Hobson and Witts use venom in a concentration of 1 : 20,000. The addition of lecithin proved to accelerate the clotting rate of venom, and in a concentration of 0.5 per cent (5 mg. of lecithin to 1.0 cc. of venom solution) the substance overcomes interference with clot formation due to hemolysis, hyperlipemia and other factors, which delay coagulation if venom alone is the source of thromboplastin. Crosbie and Scarborough confirm the accelerated rate of plasma coagulation by the addition of lecithin to venom.

Miscellaneous Observations: The concentration of plasma prothrombin in normal subjects was studied by Hause and Tocantins.[521] No consistent variation occurs during menstrual cycles. They give tables based on the plasma coagulation time of normal subjects for the calculation of the prothrombin content of unknown plasma throughout a range of 25 to 400 per cent of normal. The administration of vitamin K to patients without prothrombin deficiency failed to cause significant change

516. Ferguson, J. H., and Glazko, A. J.: Heparin and Natural Antiprothrombin in Relation to Activation and Assay of Prothrombin, Am. J. Physiol. **134**:47, 1941. Glazko, A. J., and Ferguson, J. H.: Quantitative Effects of Immediate Antithrombin, ibid. **134**:54, 1941.

517. Ferguson, J. H.: Stability of Prothrombin in Presence of Thrombin, Proc. Soc. Exper. Biol. & Med. **46**:80, 1941.

518. Page, R. C., and Russell, H. K.: Prothrombin Estimation Using Russell Viper Venom: Simple Modification of Quick's Method, J. Lab. & Clin. Med. **26**:1366, 1941.

519. Crosbie, A., and Scarborough, H.: Activation of Thromboplastin Preparations by Hemolysis and by Lecithin, Brit. M. J. **1**:268, 1941.

520. Hobson, F. C. G., and Witts, L. J.: A Venom-Lecithin Reagent for Acceleration of the Clotting Test (Prothrombin Time), J. Path. & Bact. **52**:367, 1941.

521. Hause, W. A., and Tocantins, L. M.: Determination of Plasma Prothrombin Variations in Normal Men and Women, Am. J. Clin. Path. **11**:54, 1941.

(Rhoads and Norris [522]). Quick [523] assigned a unit value of 100 to the prothrombin content of rabbit's blood. On this scale, that of human blood is given as 20. The prothrombin content of turtle blood is reported by Brambel and Ehrlich [524] to be higher than mammalian values. The prothrombin and the fibrinogen content of the lymph of dogs is one-half the plasma concentration, according to Brinkhous and Walker.[525] Barnes [526] observed no significant alterations of the blood prothrombin content of animals after roentgen irradiation in large and repeated doses. No interference with the absorption of vitamin K compounds by chicks was caused by the oral administration of aluminum hydroxide, according to Fliegelman, Panzer and Rhoads.[527]

Wide variations in the prothrombin content of stored citrated blood and plasma are reported by different investigators. A progressive decline is observed by most of them, although values up to 40 per cent of normal at the end of four months and 100 per cent up to thirteen days are reported by Drew and Scudder.[528] More rapid disappearance of prothrombin was found by Karabin, Udesky and Seed.[529] They report a level of 54 per cent of normal at the end of ten days. The temperature at which blood is stored exerts an important effect on the rate of prothrombin disappearance; according to Rhoads, Warren and Panzer,[439] the rate of disappearance is more rapid at 37 C. than at 4 C.

After the intramuscular injection into dogs of 0.125 to 0.50 Gm. of sodium citrate per kilogram, the prothrombin time determined according to the method of Quick is said by Shafiroff and co-workers [530] to

522. Rhoads, J. E., and Norris, R. F.: Effect of Vitamin K Therapy on Plasma Prothrombin Level of Patients Without Prothrombin Deficiency, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **17**:379, 1941.

523. Quick, A. J.: The Prothrombin Concentration (Determined by the Quick Method) of Various Species, Am. J. Physiol. **132**:239, 1941.

524. Brambel, C. E., and Ehrlich, D.: The Prothrombin Activity of Turtle Blood and the Effect of Synthetic Vitamin K Derivatives, J. Cell. & Comp. Physiol. **18**:221, 1941.

525. Brinkhous, K. M., and Walker, S. A.: Prothrombin and Fibrinogen in Lymph, Am. J. Physiol. **132**:666, 1941.

526. Barnes, W. A.: Prothrombin Formation Following Injury of Bone Marrow by Roentgen Rays, Am. J. Roentgenol. **46**:356, 1941.

527. Fliegelman, M. T.; Panzer, L. M., and Rhoads, J. E.: Effect of Colloidal Aluminum Hydroxide on Certain Aspects of Blood Coagulation, Surgery **10**:387, 1941.

528. Drew, C. R., and Scudder, J.: Studies in Blood Preservation: Fats of Cellular Elements and Prothrombin in Citrated Blood, J. Lab. & Clin. Med. **26**:1473, 1941.

529. Karabin, J. E.; Udesky, H., and Seed, L.: Effect of Stored Citrated Blood Transfusions on Patients with Hypoprothrombinemia, Surg., Gynec. & Obst. **73**:10, 1941.

(Footnotes continued on next page)

be prolonged. The volume of solution containing the salt was about 50 cc., and the solution was therefore hypertonic. Quick [531] using the same technic observed no such effect.

Studies on the identity of prothrombin by the Tiselius method for obtaining the electrophoretic pattern of plasma proteins are reported by Orr and Moore.[532] A chemical method for the purification of prothrombin obtained from beef plasma was devised by Seegers and Smith.[533]

Some colorimetric reactions of substances possessing vitamin K activity are given by Irreverre and Sullivan,[534] Novelli,[535] Scudi,[536] and Berlin.[537]

Almquist [538] reviews the methods of bioassay of vitamin K compounds, and the biologic unit assigned to active compounds is discussed by Ansbacher.[539]

BLOOD CHANGES ASSOCIATED WITH VARIOUS DISORDERS

Infection.—The diagnosis of acute appendicitis frequently taxes the acumen of the surgeon to the extreme. For aid he often turns to the blood laboratory for a "white count." The value of the leukocyte count in making a diagnosis of acute appendicitis was investigated by Smith [540] in a series of 93 cases. He finds that in 20 per cent of the cases of acute appendicitis and in fully half of the cases of subacute and chronic appendicitis the number of leukocytes and of neutrophils in the peripheral

530. Shafiroff, B. G. P.; Doubilet, H., and Co Tui: Effect of Intramuscular Injection of Sodium Citrate on Prothrombin Time of the Blood, Proc. Soc. Exper. Biol. & Med. **46**:136, 1941.

531. Quick, A. J.: Prothrombin Level of Blood After Intramuscular Injection of Sodium Citrate, Proc. Soc. Exper. Biol. & Med. **47**:1, 1941.

532. Orr, W. F., Jr., and Moore, D. H.: Studies on Identity of Prothrombin, Proc. Soc. Exper. Biol. & Med. **46**:357, 1941.

533. Seegers, W. H., and Smith, H. P.: Purification of Prothrombin, J. Biol. Chem. **140**:677, 1941.

534. Irreverre, F., and Sullivan, M. X.: A Colorimetric Test for Vitamin K, Science **94**:497, 1941.

535. Novelli, A.: A Sensitive Color Reaction for 2-Methyl-1, 4-Naphthoquinone and Related Compounds, Science **93**:358, 1941.

536. Scudi, J. V.: A Colorimetric Redox Method for Determination of Vitamin K_1 and Similar Quinones, Am. J. Physiol. **133**:440, 1941.

537. Berlin, H.: Simple Method for Determination of 2-Methyl-1, 4-Naphthohydroquinone Diacetate, a Substance Exhibiting Vitamin K Activity, Svensk. kem. tidskr. **52**:233, 1940; abstracted, Nutrition Abstr. & Rev. **11**:209, 1941.

538. Almquist, H. J.: Report on Vitamin K Assay by Curative Biological Test, J. A. Official Agric. Chemists **24**:405, 1941.

539. Ansbacher, S.: Editorial Review: Bioassay of Vitamin K, J. Nutrition **21**:1, 1941.

540. Smith, C. G.: Value of Leukocyte and Differential Count in Diagnosis of Appendicitis, Am. J. Clin. Path. **11**:713, 1941.

blood may be normal. He advises surgeons not to be unduly influenced by normal leukocyte and differential counts.

The use of the Medlar index for prognostication in cases of tuberculous infection is evaluated by Stanbury and Rae,[541] who correlated the progress of 1,401 hospitalized tuberculous patients with their Medlar index at the time of admission. They found that patients with minimal disease show a favorable type of index, while those with far advanced infection predominate in the group with unfavorable indexes. However, patients with favorable indexes tended to improve, regardless of the extent of their tuberculous lesions.

Brown and Otto[542] report confirmatory evidence of eosinophilia occurring early in the course of hookworm infection. Later, if the patient becomes debilitated, the eosinophil count may decrease. In regions in which hookworm infection is endemic a high percentage of eosinophils may be found in persons whose stools do not contain hookworm ova.

In their study of trichinosis Della Vida and Dyke[543] noted that moderate leukocytosis develops at the onset of symptoms and lasts three to four weeks. Secondary leukocytosis occurs later and reaches a maximum in the eleventh week of the disease. Eosinophilia makes its appearance after seven days of symptoms, reaching levels of 20 to 50 per cent. It tapers off by the end of the fourth week and, like the total leukocyte count, shows a secondary rise in the eleventh week of illness. The percentage of lymphocytes remains normal or below normal until the fifth week, when there is a gradual rise through the eleventh week followed by a decline again to normal values. The levels of monocytes and basophils are below normal but tend to rise slightly about the fourth week. The authors correlate the blood findings with the clinical picture as follows: During the first week there is no eosinophilia because these cells are fixed about invading parasites. By the second week surplus eosinophils have been produced, and eosinophilia appears. The cells then decrease while encystment takes place, being grouped about the parasites in the tissue. The secondary rise of the eleventh week represents the liberation of eosinophils from the tissue after encystment has been completed.

Vryonis[544] has carried out extensive studies on erythropoiesis in malaria. He finds that reticulocytosis develops about eight days after

541. Stanbury, W. S., and Rae, M. V.: The Medlar Index in Pulmonary Tuberculosis, Am. Rev. Tuberc. **44**:710, 1941.

542. Brown, H. W., and Otto, G. F.: Differential Leukocyte Count Associated with Hookworm Infection, Am. J. Dis. Child. **61**:727 (April) 1941.

543. Della Vida, B. L., and Dyke, S. C.: Blood Picture in Trichiniasis, Lancet, **2**:69, 1941.

544. Vryonis, G.: Blood Studies in Malaria: Genesis of Blood Cells in Relation to Treatment with Quinine, Am. J. M. Sc. **200**:809, 1940.

the start of quinine therapy, at which time the asexual parasites have disappeared from the blood. The peak of reticulocytosis occurs three days later, and 400,000 to 600,000 cells per cubic millimeter remain in the peripheral blood for seven to nine days. At the time of the reticulocyte peak (eleven days after treatment is started) the red cell count has fallen to its minimum and remains depressed for another week, until the reticulocyte response declines. Subsequently, the red cell count gradually rises to normal. The leukocyte count varies from 7,000 to 16,000 early in the course of therapy. At the time of the reticulocyte peak, on the eleventh day of therapy, the white cell count starts falling and reaches leukocytopenic levels. Neutropenia develops, which lasts until the end of the reticulocyte response (nineteenth day), at which time the neutrophil count again increases to normal and in addition eosinophilia appears. The author believes that erythropoiesis commences after the disappearance of parasitic toxins, while the leukocytopenia is related to a phase of hemopoiesis and not to quinine therapy, since the drug was administered well after the period of white cell decline.

Considerable work has appeared concerning the technic and clinical uses of the erythrocyte sedimentation rate. Wilder [545] has modified the Westergren apparatus and finds it useful in office practice for aid in the diagnosis of rheumatic fever, infectious arthritis, pelvic inflammatory disease, etc. Herzog [546] has used the microsedimentation method of Landow on 405 youthful patients with cardiac disease. Details of the technic are explained. He believes that the upper limits of normal by this method are 18 mm. per hour. Glazer [547] reports a simplified Westergren technic. Agnor [548] analyzes statistics obtained on his series of 2,063 patients. He advocates the use of the blood sedimentation rate as a routine diagnostic laboratory procedure. Sappington and Gillis [549] have used heparin in 1 per cent solution as an anticoagulant and have found that higher sedimentation rates are obtained with heparin than with oxalate solution. These authors suggest that the use of heparin might be advantageous in the Cutler method. Lesser and Kaufman [550] have encountered normal erythrocyte sedimentation rates in 90 per cent of

545. Wilder, G. B.: Sedimentation Rate of Red Blood Cells: A Simple Office Procedure, with Some Observations from One Thousand Consecutive Office Tests, J. Indiana M. A. **34**:24, 1941.

546. Herzog, R. S.: The Microsedimentation Rate, J. Lab. & Clin. Med. **27**:355, 1941.

547. Glazer, A. M.: A Simplified Westergren Sedimentation Rate Technique, J. Lab. & Clin. Med. **26**:1516, 1941.

548. Agnor, E. B.: Blood Sedimentation Test as Routine Diagnostic Procedure: A Clinical Evaluation of 2,063 Cases, Ann. Int. Med. **14**:774, 1940.

549. Sappington, S. W., and Gillis, L. M.: Heparin as the Anticoagulant in Sedimentation Tests: Comparative Study, Am. J. Clin. Path. **11**:83, 1941.

550. Lesser, A., and Kaufman, L. R.: Five Year Survey of Blood Sedimentation Test in Acute Appendicitis, Surg., Gynec. & Obst. **73**:163, 1941.

117 cases of acute appendicitis. They believe that this test may be of differential diagnostic value in appendicitis. Fetter and Schnabel [551] failed to observe any significant change in the erythrocyte sedimentation rates during and immediately after fever therapy for dementia paralytica, rheumatoid arthritis, gonococcic arthritis, Sydenham's chorea, ulcerative colitis, rheumatic fever and multiple sclerosis. Altogether 41 patients were studied by them.

In the absence of demonstrable disease 92 per cent of 327 young girls had sedimentation rates between 2 and 13 mm. per hour determined by the Cutler method, according to Benson and Rogers.[552]

Wardle [553] has undertaken experimental studies to determine the reason for the macrocytic type of anemia occurring in persons with Diphyllobothrium latum infection. He investigated the clue first offered in 1907, by Faust and Tallquist, who suggested that disintegration products of the tapeworm might be responsible. The author fed lipid fractions extracted from fish tapeworms to normal rabbits and found that the unsaturated fatty acid derivative caused decrease in the erythrocyte and the leukocyte level and an increase in the mean corpuscular volume of the red cells. Fatty acids derived from other sources (oleic acid, stearic acid, etc.) did not have this effect on the blood of rabbits.

From his studies on immunization and virulent infection in tuberculosis in guinea pigs, Birkhaug [554] concludes that the monocyte-lymphocyte ratio and the percentage of monocytes of the peripheral blood are the best indicators of advancing tuberculosis. The earliest response to a tuberculous infection is an increase in monocytes followed shortly by lymphocytopenia.

Endocrine Dyscrasias.—Turley and Richter [555] have shown that doses of 1 to 4 grains (0.06 to 0.26 G.n.) of thyroid kill guinea pigs within a few days. If aleuronat (a wheat flour made of aleurone, containing largely protein matter and little starch), a substance which produces lymphocytosis by an unknown mechanism, is administered simultaneously with the large dose of thyroid the guinea pigs do not die. These authors suggest that the artificially produced lymphocytosis somehow protects

551. Fetter, F., and Schnabel, T. G.: Behavior of Blood Sedimentation Rate During and After Fever Therapy, Am. J. M. Sc. **201**:115, 1941.

552. Benson, L., and Rogers, E. J.: Blood Sedimentation Rate in Healthy Girls, J. Lab. & Clin. Med. **26**:987, 1941.

553. Wardle, R. A.: Tapeworm Anemia: Influence of Tapeworm Fatty Acid upon the Host Blood Picture, Tr. Roy. Soc. Canada **35** (sect. 5):85, 1941.

554. Birkhaug, K.: Allergy and Immunity (Iathergy) in Experimental Tuberculosis: Variations in the Blood Cells of Guinea Pigs Prevented from Ever Becoming Allergic During Immunization with BCG-in-Solid-Paraffin and During Virulent Infection, Acta tuberc. Scandinav. **15**:59, 1941.

555. Turley, L. A., and Richter, K. M.: Experimental Study of the Lymphocytic Response in Thyrotoxicosis, J. Lab. & Clin. Med. **27**:1, 1941.

the animals against extreme thyrotoxicosis. They do not believe that thyroid reacts directly with aleuronat to neutralize the toxic effect.

Vollmer, Gordon, Levenstein and Charipper [556] suggest that the gonadal hormones may account for the sex differences noted in red cell and hemoglobin levels in many species. This is based on the results of experiments on normal, castrated and hypophysectomized rats.

Castrodale, Bierbaum, Helwig and MacBryde [343] administered large equivalent doses of diethylstilbestrol and estradiol to male and female dogs orally and parenterally. Thrombopenia and hemorrhage occurred after either drug was given but more promptly after estradiol. The bone marrow showed an early increase in the number of myeloid elements, followed in some cases by a phase of hypoplasia, reflected in the blood picture by development of anemia, leukocytopenia and thrombopenia. On the other hand, Tyslowitz and Hartman [557] found no toxic hematologic effects after administering large doses of estrogens (estradiol and estrone [theelin]) to rhesus monkeys.

Meyer, Thewlis and Rusch [558] have investigated the relation of the hypophysis to hemopoiesis in rats by removal of various glands of internal secretion and by administration of endocrine and nonspecific substances. They conclude that the hypophysis influences blood formation but that the effect is probably dependent not on a specific hormone but on general metabolic changes.

Malignant Growths.—Gruner [559] has studied the total white cell and the differential count at intervals after irradiation in patients with various types of tumors. He found that certain abnormalities of the circulating white cells tended to reappear persistently near the end of thirty-three week cycles and tended to wane in the middle of the cycle. The abnormalities noted were leukocytosis (up to 12,000 cells), monocytosis and lymphocytopenia. Bizarre nuclei and inclusion bodies were observed in the monocytes. Metastatic lesions also tended to manifest themselves at the end of cycles of thirty-three weeks or multiples of thirty-three weeks. This phenomenon was first described by Webster in 1938. Therefore, a periodicity of the malignant tumor with thirty-three week cycles of activity may be reflected by leukocyte abnormalities.

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556. Vollmer, E. P.; Gordon, A. S.; Levenstein, I., and Charipper, H. A.: Effects of Sex and Gonadotropic Hormones on Red Cell Counts of Rats, Proc. Soc. Exper. Biol. & Med. **46**:409, 1941.

557. Tyslowitz, R., and Hartman, C. G.: Influence of Large Doses of Estrogens on the Blood Picture of Rhesus Monkeys (Macaca Mulatta), Endocrinology **29**:349, 1941.

558. Meyer, O. O.; Thewlis, E. W., and Rusch, H. P.: The Hypophysis and Hemopoiesis, Endocrinology **27**:932, 1940.

559. Gruner, O. C.: Periodic Fluctuations in Blood Picture in Cancer and Their Bearing on Radiation Therapy, Canad. M. A. J. **44**:256, 1941.

Feldman [560] has noted that although the sedimentation rate of erythrocytes usually tends to decrease as the blood ages, in cases of Hodgkin's disease and malignant tumors the sedimentation rate of blood determined twenty-four hours after venipuncture equals or exceeds the measurement obtained when the blood is freshly drawn. This phenomenon is termed "maintenance of sedimentation rate." Of 118 patients with proved malignant growths, 96 per cent "maintained" their sedimentation rate for the twenty-four hour period, whereas of 55 patients with increased rate of erythrocyte sedimentation not due to a malignant growth, absence of the "maintenance" was observed in 95 per cent. The technic is given in detail.

In rat and mouse experiments both with benign and with malignant types of tumors, there developed an elevation of the white cell count which depended on the organismal differential of hosts and transplants, according to Blumenthal.[561] When homoisotransplants attain a large size, the animals become debilitated and anemia develops, with secondary hyperplasia of the marrow. Ohga, Jo and Fujii [562] produced anemia by bleeding in healthy dogs and in others with sarcoma tumors. They found that the dogs with sarcoma regenerated red cells and hemoglobin more slowly than the normal animals. They demonstrated that in their experiments the bone marrow was not actually invaded by a malignant growth but that the poor erythropoiesis was most likely explained on the basis of toxic changes which made the whole organism less efficient.

Chemical Intoxication.—The blood abnormalities most commonly encountered in workers exposed to benzene are listed by Goldwater [563] as anemia with relatively high hemoglobin values, thrombopenia and, occasionally, leukocytopenia. Goldwater and Tewksbury,[564] who studied over 100 subjects, found some of these effects to persist for as long as two years after exposure. Schwarz and Teleky [565] observed thrombopenia as an early sign of toxicity in workers exposed to benzene.

560. Feldman, H.: Maintenance of the Sedimentation Rate of Erythrocytes in Vitro in Cases of Malignant Tumors and Hodgkin's Disease, Am. J. M. Sc. **200**:820, 1940.

561. Blumenthal, H. T.: Effects of Spontaneous and Transplanted Rat and Mouse Tumors on the Red and White Cells in Circulating Blood and Bone Marrow, Cancer Research **1**:196, 1941.

562. Ohga, T.; Jo, S., and Fujii, Y.: Einflüsse der malignen Geschwülste auf die hämatopoetischen Organen; Einfluss der malignen Geschwülste auf die Genesung von der künstlichen Anämie, Taiwan Igakkai Zassi **40**:1254, 1941.

563. Goldwater, L. J.: Disturbances in Blood Following Exposure to Benzol, J. Lab. & Clin. Med. **26**:957, 1941.

564. Goldwater, L. J., and Tewksbury, M. P.: Recovery Following Exposure to Benzene (Benzol), J. Indust. Hyg. & Toxicol. **23**:217, 1941.

565. Schwarz, E., and Teleky, L.: Some Facts and Reflections on Problem of Poisoning by Benzene and Its Homologs, J. Indust. Hyg. & Toxicol. **23**:1, 1941.

Hamilton-Paterson,[566] in a review of the literature, concludes that leukocytopenia and anemia occur most frequently in chronic intoxication. Aubertin [567] reaches the same conclusion in a similar review. The destructive action of benzene on the bone marrow is particularly emphasized by the two last-named authors.

Schrenk and his collaborators [568] found the highest concentration of benzene in the fat and the bone marrow of dogs exposed to toxic fumes of benzene. The concentration of benzene was twenty times greater in the bone marrow than in the peripheral blood. In rabbits a fall in the red cell count two hours after exposure to benzene vapor was noted by Robinson and Climenko.[569] Latta and Davies [570] noted in rats an initial stimulation of granulopoiesis in the bone marrow after exposure to benzene fumes. Large or repeated exposure caused granulocytopenia and in time aplastic bone marrow.

Lead hazards in the printing industry were studied by Ruf and Belknap [571] and by Kehoe.[572] No appreciable lead hazard was found in the case of workers in the composing room. After exposures of five years, no blood abnormalities were observed in 40 subjects studied by Ruf and Belknap. Kammer [573] examined 250 workers in the lead-bearing steel (ledloy) industry. No evidence of plumbism was found in the blood or the urine or by physical examination.

Marchmont-Robinson [574] determined the urinary excretion of lead in workers exposed to lead dust. He observed a significant clinical regres-

566. Hamilton-Paterson, J. L.: Chronic Benzene Poisoning, Lancet **1**:73, 1941.

567. Aubertin, C.: Le benzène, agent leucolytique, Paris méd. **2**:504, 1940.

568. Schrenk, H. H., and others: Absorption, Distribution and Elimination of Benzene by Body Tissues and Fluids of Dogs Exposed to Benzene Vapor, J. Indust. Hyg. & Toxicol. **23**:20, 1941.

569. Robinson, E. J., and Climenko, D. R.: Effects of Inhalation of Benzene Vapors on Red Blood Cells of Rabbits, J. Indust. Hyg. & Toxicol. **23**:232, 1941.

570. Latta, J. S., and Davies, L. T.: Effects on Blood and Hemopoietic Organs of Albino Rat of Repeated Administration of Benzene, Arch. Path. **31**:55 (Jan.) 1941.

571. Ruf, H. W., and Belknap, E. L.: Studies on the Lead Hazards in Certain Phases of Printing: I. Actual Lead Exposures as Measured by the Amount of Lead in Printing Atmospheres; II. Actual Lead Absorption as Measured by Physical Examinations, Blood and Urine Studies, J. Indust. Hyg. & Toxicol. **22**:445, 1940.

572. Kehoe, R. A.: Note on "Studies of the Lead Hazards in Certain Phases of Printing," J. Indust. Hyg. & Toxicol. **23**:159, 1941.

573. Kammer, A. G.: Studies of Workers Exposed During Production of Lead Bearing Steel (Ledloy), J. Indust. Hyg. & Toxicol. **23**:93, 1941.

574. Marchmont-Robinson, S. W.: Effect of Vitamin C on Workers Exposed to Lead Dust, J. Lab. & Clin. Med. **26**:1478, 1941.

sion of symptoms and a slight increase in lead excretion after the daily oral administration of 50 mg. of ascorbic acid. The author suggests that many of the vague symptoms associated with chronic plumbism are evidences of subclinical scurvy. The presence of lead may interfere with vitamin C absorption, and the author suggests that a vitamin C deficiency may be prevented by increasing the ascorbic acid intake. Kety and Letonoff,[575] in a preliminary report, noted rapid disappearance of toxic symptoms in patients with lead poisoning who were given sodium citrate by mouth. The administration of 6 to 12 Gm. in divided daily doses was followed by a fall in the concentration of lead in the blood in all cases.

Industrial manganese poisoning is accompanied by leukocytopenia with neutropenia, according to Flinn, Neal and Fulton.[576] The authors observed normal red cell and platelet counts in the 50 workers studied.

Brieger [577] reviews the literature of carbon disulfide intoxication. He concludes that further study is needed before this agent is classed as a blood intoxicant.

The increased use of thiocyanate preparations in clinical medicine prompted Lindberg, Wald and Barker [578] to undertake toxicologic studies of this agent on dogs. Potassium thiocyanate was given orally to 12 dogs in amounts sufficient to raise the blood level to 20 to 60 mg. per hundred cubic centimeters. For human beings a level of 8 to 14 mg. per hundred cubic centimeters is considered safe. Severe microcytic, hypochromic anemia developed in the animals, while the white cell and differential counts, red cell fragility and icterus index were unaffected. Blood cholesterol and serum protein values decreased, and the color index and the volume index of red cells fell below 0.8. Pathologic examination revealed damage of the bone marrow and the liver.

METHODS AND MISCELLANEOUS MATERIAL

The structure and properties of the human erythrocyte are discussed by Haden.[579] The article includes excellent bas-relief photographs of red

575. Kety, S. S., and Letonoff, T. V.: Treatment of Lead Poisoning with Sodium Citrate, Proc. Soc. Exper. Biol. & Med. **46**:476, 1941.

576. Flinn, R. H.; Neal, P. A., and Fulton, W. B.: Industrial Manganese Poisoning, J. Indust. Hyg. & Toxicol. **23**:374, 1941.

577. Brieger, H.: Effects of Carbon Disulfide on Blood Corpuscles, J. Indust. Hyg. & Toxicol. **23**:388, 1941.

578. Lindberg, H. A.: Wald, M. H., and Barker, M. H.: Observations on Pathologic Effects of Thiocyanate: Experimental Study, Am. Heart J. **21**:605, 1941.

579. Haden, R. L.: Human Red Blood Cell (Porter Lecture), Cleveland Clin. Quart. **8**:111, 1941.

cells. The following formula is suggested by Vallarino [580] as an improved dilution fluid for the enumeration of erythrocytes: iodine, 0.3 per cent; potassium iodide, 0.4 per cent; sodium citrate ($Na_3C_6H_5O_7.2H_2O$), 1 per cent; add distilled water to 100 cc., and filter. A study of some of the factors involved in calculating erythrocyte counts and percentage volume by opacimetry is reported by Ponder.[581] He states that opacity is a function of several variables and that prediction of counts is poor, even in the case of normal blood. The standard error of discrepancies between the count obtained by enumeration and that secured by opacimetry is about ± 500,000 and that for the percentage volume is about ± 2.7 units of volume. For opacity measurements an isotonic solution of sodium citrate with a 0.1 per cent solution of formaldehyde U. S. P. is preferable to an isotonic solution of sodium chloride, but only because the variations in light transmission which accompany stirring are greatly lessened. The stirring effects seem to be due to the orientation of masses of cells by currents in the suspension medium.

The measurement of red cell diameter by a diffractometric method is reported by Smith.[582] A simple device attached to an ordinary microscope was employed. The results obtained on the same specimens of blood by two examiners were in reasonably close agreement. A micromethod for the determination of erythrocyte fragility which involves the use of only six concentrations of sodium chloride is described by Kato.[583] Greatly increased fragility of red cells was observed in an infant with erythroblastosis foetalis. As the number of circulating nucleated erythrocytes was reduced, the resistance of the red cells to hypotonic solution of sodium chloride became normal.

The circulating and the total red cell volume of dogs have been measured by Hahn and his associates [584] with the aid of radioactive iron. The red cell mass calculated by means of this isotope averages about 20 per cent less than the value obtained from determinations of the plasma volume and the hematocrit reading of blood from the jugular vein. A

580. Vallarino, L. A.: An Improved Dilution Fluid for Erythrocyte Counts, Stain Technol. **16**:177, 1941.

581. Ponder, E.: Red Cell Counts, Percentage Volume, and Opacity of Suspensions, Am. J. Physiol. **134**:739, 1941.

582. Smith, K. E.: The Measurement of Red Blood Cell Diameter by the Diffractometer, J. Lab. & Clin. Med. **26**:696, 1941.

583. Kato, K.: A Simple and Accurate Microfragility Test for Measuring Erythrocyte Resistance: A Combination Microhemopipette Method, J. Lab. & Clin. Med. **26**:703, 1941.

584. Hahn, P. F.; Balfour, W. M.; Ross, J. F.; Bale, W. F., and Whipple, G. H.: Red Cell Volume Circulating and Total as Determined by Radio Iron, Science **93**:87, 1941.

number of articles dealing with the determination of plasma and of total blood volume, the cell-plasma ratio in different parts of the circulation and the restoration of blood volume after acute blood loss have been published by Stead, Ebert and Gibson.[585] Adequate consideration of their data would require more space than can be devoted to the subject in this review, and the interested reader will find it profitable to consult the original articles. Brines, Gibson and Kunkel [586] state that the total blood volume at birth is about 300 cc. During the first year the quantity of circulating blood is doubled, and thenceforth the volume increases to a value of about 2,500 cc. for both sexes at puberty. The plasma and the total blood volume bear a closer relation to size than to age. The unit volume per kilogram of body weight or square meter of surface area is not a constant but increases with growth. The plasma, the red cell and the total blood volume may be predicted, according to the authors, in the case of normal infants and children, on the basis of height, weight or surface area. A method for the measurement of red cell volume in blood by the use of Evans blue dye is described by Shohl and Hunter.[587]

A study of the familial incidence of elliptic erythrocytes is reported by Wyandt, Bancroft and Winship.[588] The authors observed the peculiarly shaped red cells in the blood of 86 members of 3 interrelated families of pure German extraction. In 1 member only of each of 2 pairs of twins were oval erythrocytes found. Aspiration of sternal marrow performed on 2 subjects with ovalocytosis revealed spherical nucleated erythrocytes. The evidence indicates that the change to an elliptic form occurs during or after the reticulocyte stage of development. The red cell abnormality is compatible with long life and is not correlated with the incidence of any recognized disease.

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585. Stead, E. A., Jr., and Ebert, R. V.: Relationship of the Plasma Volume and the Cell Plasma Ratio to the Total Red Cell Volume, Am. J. Physiol. **132**:411, 1941. Ebert, R. V., and Stead, E. A., Jr.: Demonstration That the Cell Plasma Ratio of Blood Contained in Minute Vessels Is Lower Than That of Venous Blood, J. Clin. Investigation **20**:317, 1941. Ebert, R. V.; Stead, E. A., Jr., and Gibson, J. G., II: Response of Normal Subjects to Acute Blood Loss, with Special Reference to the Mechanism of Restoration of Blood Volume, Arch. Int. Med. **68**:578 (Sept.) 1941. Ebert, K. V., and Stead, E. A., Jr.: An Error in Measuring Changes in Plasma Volume After Exercise, Proc. Soc. Exper. Biol. & Med. **46**: 139, 1941.

586. Brines, J. K.; Gibson, J. G., II, and Kunkel, P.: The Blood Volume in Normal Infants and Children, J. Pediat. **18**:447, 1941.

587. Shohl, A. T., and Hunter, T. H.: The Measurement of Cell Volume of Blood by the Evans Blue Dye Method, J. Lab. & Clin. Med. **26**:1829, 1941.

588. Wyandt, H.; Bancroft, P. M., and Winship, T. O.: Elliptic Erythrocytes in Man, Arch. Int. Med. **68**:1043 (Dec.) 1941.

A genetic study of persons with oval red cells was carried out by Burks and Wyandt.[589] They report the possibility of incomplete sex linkage between oval cells and the presence of AB agglutinogens.

Erythrocytes which show blue granules when treated with potassium ferrocyanide and hydrochloric acid, the prussian blue reaction, are described by Grüneberg.[590] Such granules are found in the cells of mouse and rat embryos, and after birth about 4 per cent of the circulating erythrocytes contain them. Large numbers of the granular erythrocytes were found in mice with the recessive gene for flexed tail and belly spot associated with normocytic anemia.

A comparison of various methods of hemoglobin determination was made by Karr and Clark,[591] and many of the results obtained were considered grossly inaccurate. Standardized photoelectric methods are recommended. Barkan [592] describes a method for the estimation of hemoglobin by the use of undiluted reduced blood, which avoids errors due to variations of the time of reading. The hemoglobin contents of ear and of finger blood were compared with that of venous blood by Sørensen.[593] Samples removed immediately after ear puncture were, in general, found to yield erroneously high results, and more accurate determinations were made on blood from the finger. Isaacs [594] proposes that the quantity of hemoglobin expressed in grams per hundred cubic centimeters be multiplied by the factor 3 and the product divided by the erythrocyte count expressed in hundreds of thousands per cubic millimeter, in order to obtain an index possessing the same significance as the color index, but not requiring conversion of absolute values to percentages. A commonly employed and more accurate method of rapidly securing an approximation of the color index consists of dividing

589. Burks, B. S., and Wyandt, H.: Oval Blood Cells in Human Subjects Tested for Linkage with Taste for PTC, Mid-Digital Hair, Hair Color, AB Agglutinogens and Sex, Genetics **26**:223, 1941.

590. Grüneberg, H.: Siderocytes: New Kind of Erythrocytes, Nature, London **148**:114, 1941.

591. Karr, W. G., and Clark, J. H.: Comparison of Various Hemoglobin Methods as Performed in Hospital and Physicians' Laboratories, Am. J. Clin. Path., Tech. Supp. **5**:127, 1941.

592. Barkan, G.: Hemoglobin Estimation with Undiluted Reduced Blood, J. Lab. & Clin. Med. **26**:1823, 1941.

593. Sørensen, G.: Variations in the Hemoglobin Content of Capillary Blood and Their Significance in the Technique of Hemoglobin Determination, Nord. med. (Hospitalstid.) **10**:1117, 1941; abstracted, Nutrition Abstr. & Rev. **11**:185, 1941.

594. Isaacs, R.: Simple Hemoglobin-Red Blood Cell Ratio to Replace Color Index, J. A. M. A. **116**:2258 (May 17) 1941.

the gram value of hemoglobin per hundred cubic centimeters of blood by three times the erythrocyte count expressed in millions per cubic millimeter.

Ramsey [595] reports evidence of two types of hemoglobin in the blood of various mammals, birds, reptiles and amphibia. The types differ in their resistance to alkaline denaturation. Denaturation was hastened either by increasing the degree of alkalinity or by raising the temperature of the medium.

Values for the concentration of hemoglobin in the blood are reported by Wardlaw [596] and by Meccheri [597] for normal men and by Ta [598] for women in India. Hematologic values in elderly patients are reported by Fowler and his co-workers.[599] Less difference between the sexes was observed in them than is encountered in younger persons, and presence or absence of gastric hydrochloric acid seemed not to be related to the observed blood levels.

Changes in the white cell count during labor and in the early postpartum period were investigated by Wolff.[600] He observed progressive leukocytosis, which appeared to be related to uterine contractions, since no rise occurred during periods of inertia of the uterus.

In 4 of 8 cases of gargoylism Reilly [601] noted peculiar granules in the white cells. The neutrophils were most often affected, but similar changes were also found in lymphocytes and monocytes. When stained with Wright's stain such granules were usually larger than those of normal neutrophils and were tinted lilac blue, but in some cells eosinophilic granules, smaller and less refractile than those of normal eosinophils, were observed. The granules were found in cells contained within the peripheral blood, the bone marrow and the spleen. The author suggests that they may represent a type of toxic reaction.

Blood studies made on a series of patients with intestinal obstruction revealed leukocytopenia developing at some time during the first week

595. Ramsey, H. J.: A Comparative Study of Hemoglobin Denaturation, J. Cell. & Comp. Physiol. **18**:369, 1941.

596. Wardlaw, H. S. H.: Concentration of Haemoglobin in Blood of Normal Men, M. J. Australia **2**:103, 1941.

597. Meccheri, L. A.: Blood Hemoglobin Concentration in Healthy Persons and in Persons with Pulmonary Tuberculosis, Publ. d. Centro de invest. tisiol. **4**:83, 1940.

598. Ta, C. R.: Haematological Studies in Indians: Normal Indian Women in Calcutta, Indian J. M. Research **29**:375, 1941.

599. Fowler, W. M.; Stephens, R. L., and Stump, R. B.: Changes in Hematological Values in Elderly Patients, Am. J. Clin. Path. **11**:700, 1941.

600. Wolff, J. R.: Leukocyte Count in Labor, Am. J. Obst. & Gynec. **41**:611, 1941.

601. Reilly, W. A.: Granules in the Leukocytes in Gargoylism, Am. J. Dis. Child. **62**:489 (Sept.) 1941.

after the surgical release of such obstruction, according to Harris and Feldheym.[602] The white cell counts decreased from a moderately elevated level before operation to a range of 2,000 to 3,000 per cubic millimeter during the postoperative period. Relative neutropenia of moderate degree occurred. The changes are attributed to the presence of toxins within the obstructed bowel which are not absorbed because of capillary compression until the obstruction is released. When leukocytopenia occurs before operation, it is believed to indicate that only partial obstruction is present, thus enabling absorption of toxins to take place.

Graham and Fowler [603] state that transfused leukocytes contained in freshly obtained donors' blood disappear from the circulation of the recipient during a period of two and one-half hours. Although in stored blood the white cells undergo disintegration, the leukocyte products so formed may have a stimulative action on new white cell production. However, no definite evidences of such stimulation were observed by the authors during the observation of 15 patients with various types of infection.

Leukocytosis with a shift to younger forms of neutrophils was observed by Curphey and Ponder [604] during the course of experimentally produced shock.

The leukocytes of a number of primitive species of invertebrates, as well as those of vertebrates, were studied by George.[605] In all species examined the leukocytes appeared to exist as free cells of mesenchymal origin. In many low forms they performed the important functions of food handling and digestion, as well as possessing, in common with the white cells of higher animals, the property of phagocytosis of harmful substances. Turpin and his associates [606] studied the Arneth leukocyte formulas of a number of sets of twins. They found the same white cell patterns in both members of pairs of identical twins and varying formulas in the case of heterozygous twins.

602. Harris, F. I., and Feldheym, J. S.: Leukocyte Exhaustion in Intestinal Obstruction, Am. J. Surg. **54**:417, 1941.

603. Graham, J. A., and Fowler, W. M.: Behavior of the Recipient's Leukocyte Count Following Transfusion of Preserved Blood, J. Lab. & Clin. Med. **26**:1911, 1941.

604. Curphey, T. J., and Ponder, E.: Leukocyte Response in Experimental Shock, Am. J. Path. **17**:602, 1941.

605. George, W. C.: Comparative Hematology and the Functions of the Leukocytes, Quart. Rev. Biol. **16**:426, 1941.

606. Turpin, R.; Caratzali, A., and Piton, J.: De l'influence de l'hérédité sur la formule d'Arneth, Presse méd. **48**:538, 1940.

Consideration of the numerous articles which deal with the performance of the sedimentation test and report results obtained with this laboratory procedure are omitted from this review. An authoritative discussion of the subject of the sedimentation phenomenon and its application to clinical practice has been presented by Wintrobe.[607]

Articles dealing with the blood platelets and the factors involved in the coagulation of the blood have been reviewed in the section on hemorrhagic disorders. Diagnostic tests based on alterations of the leukocytes and studies made by aspiration of sternal marrow have likewise been considered elsewhere. Two hundred and nine articles appearing in the literature from July 1, 1939 to June 30, 1940 on the formed elements of the blood have been reviewed by Higgins.[608]

The Thomas Henry Simpson Memorial Institute for Medical Research.

607. Wintrobe, M. M.: Erythrocyte Sedimentation Test, Am. J. Clin. Path. **11**:562, 1941.

608. Higgins, G. M.: Formed Elements of Blood, Ann. Rev. Physiol. **3**:283, 1941.

Book Reviews

Diseases of the Blood and Atlas of Hematology. By Roy R. Kracke, M.D. Second edition, revised and enlarged. Price, $15. Pp. 692, with 46 illustrations and 54 colored plates. Philadelphia: J. B. Lippincott Company, 1941.

This book combines a textbook, a laboratory guide and an atlas of hematology. The material is grouped in eight sections: Hematologic Terminology, the Development and Morphology of Blood Cells, Leukocytosis and Leukopenia, the Anemias, the Leukemias, Hemorrhagic Diseases, Miscellaneous, and Hematologic Technic.

A separate chapter has been contributed by Dr. Lloyd F. Craver on the treatment of leukemia, including recent advances in the use of irradiation and radioactive isotopes. Dr. Francis P. Parker has a chapter on blood groups and blood transfusions; Dr. Elizabeth Gambrell, a chapter on malaria, and Dr. R. P. Custer, a section on bone marrow.

The first forty pages are devoted to a discussion of hematologic terminology in which the author starts a crusade for a more fundamental understanding of this perplexing problem. It is questionable if such a crusade belongs in a book of this type. In the chapter on classification of anemias, the author propounds both the morphologic classification of Osgood, Wintrobe and Haden and the clinical etiologic classification of Castle and Minot. But in the subsequent chapter the author fails to abide by either classification and groups a long list of anemias under the general heading of hypochromic anemias. This seems neither justified nor good teaching. The reviewer feels that the author should have exerted more right of editorship in regard to the contributed chapters. For example, in the chapter on bone marrow a complete repetition of the discussion of terminology, cell morphology and origin and development of cells is given, which only adds to the state of confusion that the author had so nobly attempted to straighten out in earlier chapters. The chapter on malaria, although excellent, is considerably longer than chapters on the essential anemias. The selection of bibliography is excellent, although the reviewer could mention a few outstanding omissions, particularly Bernstein's review of infectious mononucleosis, which appeared in the *Journal of Medicine*. As a whole, the reviewer feels that the book has a definite place in American hematology and certainly can be recommended.

Medical Progress, 1940: A Series of Fifty-Two Reports Published During 1940 in The New England Journal of Medicine. Edited by Robert N. Nye, M.D. Price, $4. Pp. 625. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

The reviewer has followed with interest the articles that have appeared in the *New England Journal of Medicine* dealing with advances in diagnosis and therapy in the fields in which the authors were particularly interested. These reviews have been of great value to the teacher employing them as references for reading by senior medical students. Comments from practitioners of medicine have shown that the articles have been valuable to them.

It might be said that these papers, strictly speaking, are not attempts to cover all the recent literature on particular subjects. An author picks out the high spots and mentions only those contributions in current medical literature which he as a critic and one who knows his subject well can evaluate as being worth while and representing distinct advances in knowledge of diseases, functional disorders, pathologic conditions or any other aspect of the subject.

This present, or second, edition, represents in one volume the reviews (it might possibly be better to speak of them as discussions) of particular subjects which appeared in the *New England Journal of Medicine* during 1940. The book can be recommended most highly not only to the readers already mentioned but to the specialist who would be interested in a brief summary of the important contribu-

tions in specialties other than the one with which he is thoroughly familiar. The format of the book is excellent; particularly to be commended are the extensive bibliographies.

Clinical Roentgenology of Pregnancy. By William Snow, M.D., Director of Radiology, Bronx Hospital, and Roentgenologist-in-Charge, Harlem Hospital. Price, $4.50. Pp. 178, with 119 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

The author states in the preface that the roentgen study of pregnancy is fulfilling an everyday need which he claims is easily as important as the need for other major roentgen studies, such as those of the respiratory, the gastrointestinal and the urinary tract. He has prepared this book as a short text by which to make the clinical roentgenology of pregnancy more generally useful.

The seven chapters begin, by way of introduction, with a general discussion of the use of the roentgen ray in pregnancy. There is a good deal here to interest the internist.

Five following chapters deal with the more strictly technical aspects of the book's subject. The last chapter comprises case reports: On one page are roentgenograms, and on the opposite page are short case summaries, which describe exactly the manner in which each roentgenogram is to be interpreted in connection with the given history.

The entire volume is well prepared in legible type, with clear tables and good film reproductions, which are labeled plainly so as to be as understandable as possible. The author hopes that his book will be used as a working manual and as a ready reference by those interested in the roentgenology of pregnancy. In all probability this wish will be satisfied.

Cerebrospinal Fever. By Denis Brinton, D.M. (Oxon.), F.R.C.P. (Lond.). Price, $3. Pp. 172. Baltimore: Williams & Wilkins Company, 1941.

This little book from England, of some one hundred and fifty pages of text, should at the present time be of considerable importance for two reasons. In the first place, meningitis is an ever present disease which might, if the experiences of the last war are repeated, increase to large proportions in cantonments. The second reason is that the book contains a full description of the modern treatment of the disease, particularly with chemotherapeutic agents in the last two years. The reduction in the mortality of meningitis as a result of the use of sulfanilamide and its derivatives has been so remarkable that every physician should be thoroughly acquainted with methods of treatment which have already proved of such value.

Brinton discusses fully the usual features that one would expect in a systematic outline of the disease. Epidemiology, etiology, pathology, course, diagnosis and so on compose roughly about half the book. The remainder is given over to treatment. There is a rather small list of references at the end of the text. The advice that the author gives in regard to treatment is excellent; the presentation of the remainder of the various phases of cerebrospinal fever is conservative and more or less of the conventional textbook type. The book itself is well printed, and the format leaves nothing to be desired.

Neural Mechanisms in Poliomyelitis. By Howard A. Howe and David Bordian. Price, $3.50. Pp. 234, with 39 plates. New York: The Commonwealth Fund, 1942.

This important monograph by outstanding investigators in the field of poliomyelitis presents the evidence for transmission of virus on the basis both of original work and of review of the literature. The paramount importance of neural transmission even when the portal of entry is in the gastrointestinal tract is elucidated. In general, the relative importance of the respiratory tract and the alimentary tract as routes of invasion in different species of monkeys and in man is discussed, and gaps in knowledge not yet filled are pointed out. Of especial interest, of course, is the detailed account of the authors' own experiments, illustrated by many photomicrographs.

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